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# TRANSACTIONS

OF THE

# PATHOLOGICAL SOCIETY OF LONDON.

VOLUME THE FIFTY-SEVENTH.

COMPRISING THE REPORT OF THE PROCEEDINGS FOR THE SESSION 1905-1906.

THE FRANCIS A. COUNTWAY
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# Presidents of the Society.

| ELECTED | |
|---|---|
| 1846 | CHARLES J. B. WILLIAMS, M D., F.R.S. |
| 1848 | CHARLES ASTON KEY. |
| 1850 | PETER MERE LATHAM, M.D. |
| 1852 | CÆSAR H. HAWKINS, F.R.S. |
| 1853 | BENJAMIN GUY BABINGTON, M.D., F.R.S. |
| 1855 | JAMES MONCRIEFF ARNOTT, F.R.S. |
| 1857 | Sir THOMAS WATSON, Bart., M.D., F.R.S |
| 1859 | Sir WILLIAM FERGUSSON, Bart., F.R.S |
| 1861 | JAMES COPLAND, M.D., F.R.S. |
| 1863 | Sir PRESCOTT G. HEWETT, Bart., F.R.S. |
| 1865 | THOMAS BEVILL PEACOCK, M.D. |
| 1867 | Sir JOHN SIMON, K.C.B., D.C.L., F.R.S. |
| 1869 | Sir RICHARD QUAIN, Bart., M.D., LL.D., F.R.S. |
| 1871 | JOHN HILTON, F.R.S. |
| 1873 | Sir WILLIAM JENNER, Bart., M.D., G.C.B., D.C.L., F.R.S. |
| 1875 | GEORGE D. POLLOCK. |
| 1877 | CHARLES MURCHISON, M.D., LL.D., F.R.S. |
| 1879 | JONATHAN HUTCHINSON, F.R.S. |
| 1881 | Sir SAMUEL WILKS, Bart., M.D., F.R.S. |
| 1883 | JOHN WHITAKER HULKE, F.R.S. |
| 1885 | JOHN SYER BRISTOWE, M.D., F.R.S. |
| 1887 | Sir JAMES PAGET, Bart., D.C.L., LL.D., F.R.S. |
| 1889 | WILLIAM HOWSHIP DICKINSON, M.D. |
| 1891 | Sir GEORGE MURRAY HUMPHRY, M.D., LL.D., F.R.S. |
| 1893 | FREDERICK WILLIAM PAVY, M.D., LL.D., F.R.S. |
| 1895 | HENRY TRENTHAM BUTLIN, D.C.L. |
| 1897 | JOSEPH FRANK PAYNE, M.D. |
| 1899 | WILLIAM WATSON CHEYNE, C.B., F.R.S. |
| 1902 | Sir JOHN BURDON SANDERSON, Bart., M.D., D.C.L., F.R.S. |
| 1906 | PHILIP HENRY PYE-SMITH, M.D., F.R.S. |

# OFFICERS AND COUNCIL

OF THE

# Pathological Society of London,

ELECTED AT

THE GENERAL MEETING, MAY 29TH, 1906,

FOR THE SESSION 1906–1907.

## President.

P. H. PYE-SMITH, M.D., F.R.S.

## Vice-Presidents.

W. P. HERRINGHAM, M.D. (1) | F. W. PAVY, M.D., F.R.S. (3)
SIR ALMROTH WRIGHT, M.D. (2) | F. G. HOPKINS, F.R.S. (4)

## Treasurer.

H. H. CLUTTON.

## Council.

*Members of Committee of Section A.*

E. F. BUZZARD, M.D. — C. G. SELIGMANN, M.B.
J. H. DRYSDALE, M.D. — H. THURSFIELD, M.D.
F. J. POYNTON, M.D. — F. P. WEBER, M.D.
A. WHITFIELD, M.D.

*Members of Committee of Section B.*

G. DEAN, M.D. — R. T. HEWLETT, M.D.
W. D'ESTE EMERY, M.D. — T. J. HORDER, M.D.
K. W. GOADBY. — D. NABARRO, M.D.

*Members of Committee of Section C.*

C. J. MARTIN, M.D., F.R.S. — J. LORRAIN SMITH, M.D.
M. S. PEMBREY, M.D. — E. H. STARLING, M.D., F.R.S.

*Members of Committee of Section D.*

O. GRÜNBAUM, M.D. R. HUTCHISON, M.D. J. B. LEATHES, M.B.

## Sectional Secretaries.

*Section A.* G. F. STILL, M.D.
*Section B.* W. BULLOCH, M.D.
*Section C.* T. G. BRODIE, M.D., F.R.S.
*Section D.* A. E. GARROD, M.D.

## General Secretary and Editor of the 'Transactions.'

S. G. SHATTOCK.

## Trustees.

T. BRYANT, M.Ch. J. F. PAYNE, M.D. H. MORRIS, M.B.

NOTE.—Section A: Pathological Anatomy and Histology. Section B: Bacteriology. Section C: Experimental Pathology. Section D: Chemical Pathology.
(1) Chairman of Section A. (2) Chairman of Section B.
(3) Chairman of Section C. (4) Chairman of Section D.

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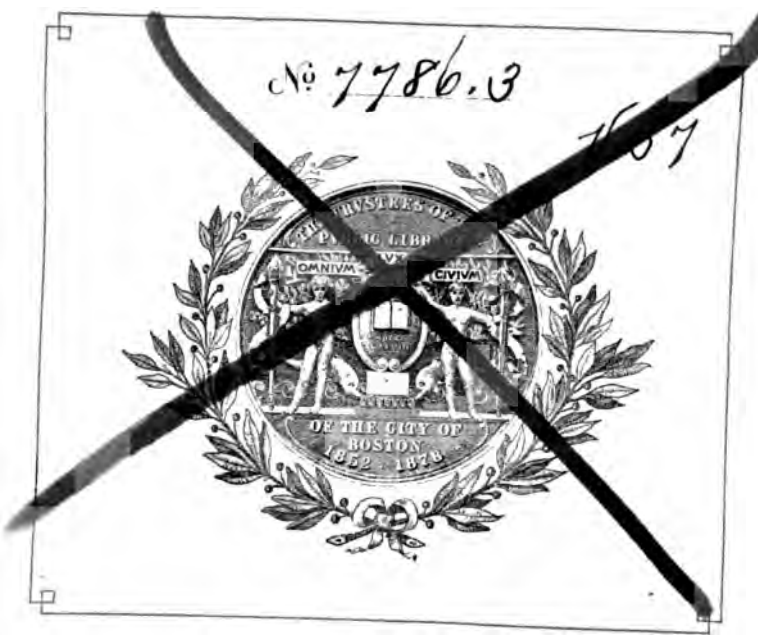

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# GENERAL LIST OF MEMBERS.

*Elected*

1879 **ABERCROMBIE**, JOHN, M.D., Augill Brough, Westmorland. (C. 1897-1900.)

1896 ABRAHAMS, BERTRAM LOUIS, B Sc., M.B., 14, Welbeck street, W.

1883 ACLAND, THEODORE DYKE, M.D., 19, Bryanston square, W. (C. 1892-4.)

1891 ADAMI, J. GEORGE, M.A., M.D., Montreal, Canada.

1890 ADAMS, JAMES, M.D., 4, Chiswick place, Eastbourne.

1848 **AIKIN**, CHARLES A., 12, Ladbroke terrace, W. (C. 1864-6.)

1872 AIKIN, CHARLES EDMUND, Llandrillo, Corwen, North Wales.

1897 ALCOCK, SAMUEL K., M.D., Portland House, Burslem.

1882 **ALLCHIN**, WILLIAM HENRY, M.D., 5, Chandos street, W.

1884 ANDERSON, ALEXANDER RICHARD, 5, East Circus street, Nottingham.

1897 ANDREWES, FREDERICK W., M.D., 31, Hampstead lane, Highgate, N. (C. 1900—6. Com. Sect. B, 1901—6.)

1902 ARMOUR, DONALD, M.B., 89, Harley street, W.

1883 ASHBY, HENRY, M.D., 13, St. John street, Manchester.

1863 BAGSHAWE, FREDERICK, M.A., M.D., 35, Warrior square, St. Leonard's-on-Sea.

1904 BAILEY, WILLIAM HENRY, M.D., Featherstone Hall, Southall, Middlesex.

1902 BAINBRIDGE, F. A., M.B., 1, Vernon Chambers, Southampton row, W.C.

1856 **Balding**, DANIEL BARLEY, Royston, Herts.

1881 BALLANCE, CHARLES A., M.S., 106, Harley street, W. (C. 1890-2. C. Com. Sect. C, 1901—4. S. 1899—1901.)

1875 BARKER, ARTHUR E. J., 87, Harley street, W. (C. 1884-6. V.P. 1896-7.)

1899 BARKER, A. J. G., Kuching, Sarawak, Borneo.

1885 BARLING, GILBERT, M.B., 87, Cornwall street, Newhall street, Birmingham. (C. 1894-7.)

1901 BARNARD, HAROLD L., M.S., 21, Wimpole street, W.

1874 **BARLOW**, Sir THOMAS, Bart., K.C.V.O., M.D., B.S., 10, Wimpole street, W. (C. 1879-81. V.-P. 1894-6.)

1899 BARRATT, JOHN OGLETHORPE WAKELIN, M.D., Thompson-Yates Laboratory, University College, Liverpool.

1877 BARROW, A. BOYCE, 8, Upper Wimpole street, W.

1881 BARRS, ALFRED GEORGE, M.D., 22, Park place, Leeds.

1853 **BARWELL**, RICHARD, 55, Wimpole street, W. (C. 1862-4. V.-P. 1889-90.)

*Elected*

1861 **BASTIAN**, H. CHARLTON, M.A., M.D., F.R.S., 8A, Manchester square, W. (C. 1869-71. V.-P. 1885-7.)

1877 BATEMAN, ARTHUR W., B.A., Tenterfield, New South Wales.

1895 BATTEN, FREDERICK E., M.D., 33, Harley street, W. (C. Com. Sect. A, 1903–5.)

1876 **BATTESON**, JOHN, 188, Goldhawk road, Shepherd's Bush.

1882 BATTLE, WILLIAM HENRY, 49, Harley street, W. (C. 1898—1901.)

1870 BÄUMLER, CHRISTIAN G. H., M.D., The University, Freiburg, in Baden Baden, Germany.

1892 BEADLES, CECIL F., The Clergy House, Englefield Green, Surrey. (C. 1898—1901.)

1879 BEALE, EDWIN CLIFFORD, M.B., 23, Upper Berkeley street, W.

1856 BEALEY, ADAM, M.D., M.A., Felsham Lodge, Hollington park, St. Leonard's-on-Sea.

1904 BEATTIE, JAMES M., M.D., Pathological Department, University of Edinburgh.

1897 BEDDARD, ARTHUR P., M.D., 44, Seymour street, W.

1865 BEEBY, WALTER, M.D., Rapollo, Liguria, Italy (Nov.—May), and Varallo Valsesia (May, June, Sept., Oct.).

1880 **BEEVOR**, CHARLES EDWARD, M.D., 135, Harley street, W. (C. 1888-90.)

1883 BENHAM, R. FITZROY, 11, Earl's Court square, S.W.

1886 BENNETT, FREDERICK JOSEPH, 17, George street, Hanover square, W.

1877 BENNETT, Sir WILLIAM HENRY, K.C.V.O., 1, Chesterfield street, W. (C. 1891-3.)

1889 BENTLEY, ARTHUR, J. M., M.D., Mena House, Pyramids, Cairo, Egypt.

1878 BERNARD, FRANCIS R., M.D., Prawls, Stone, near Tenterden, Kent.

1904 BERNSTEIN, JULIUS M., M.B., Erskine Chambers, 36, Lincoln's Inn Fields, W.C.

1882 BERRIDGE, WILLIAM ALFRED, Redhill, Surrey.

1886 BERRY, JAMES, B.S., 21, Wimpole street, W. (C. 1895-7.)

1903 BEVERIDGE, WILFRID WILLIAM OGILVIE, M.B., R.A.M.C., D.S.O., Royal Army Clothing Department, Grosvenor Road, S.W.

1856 **Bickerstoth**, EDWARD R., 2, Rodney street, Liverpool.

1882 BINDLEY, PHILIP HENRY, M.B. Address uncommunicated.

1906 BIRT, CECIL, Queen Alexandra Hospital, Millbank, S.W.

1865 BISSHOPP, JAMES, Mount Pleasant, Tunbridge Wells.

1889 BLACK, ROBERT, M.D., 14, Pavilion Parade, Brighton.

1863 BLANCHET, JEAN B., M.D., M.S., Montreal, Quebec, Canada.

1879 BOILEAU, J. P. H., M.D., Brigade-Surgeon, Army.

1900 BOKENHAM, THOMAS JESSOPP, 10, Devonshire street, Portland place, W.

1904 BOLTON, CHARLES, M.D., 16, Devonshire street, Portland place, W.

1900 BOLTON, JOSEPH SHAW, M.D., B.S., B Sc., East Sussex County Asylum, Hellingly S.O., Sussex.

1902 BONNEY, W. F. VICTOR, M.D., M.S., 30, The Manor House, Marylebone road, W.

1869 BOURNE, WALTER, M.D. (Travelling).

1861 BOWER, RICHARD NORRIS (Travelling).

*Elected*

1881 Bowlby, Anthony A., C.M.G., 24, Manchester square, W. (M.G.C. 1884—1900. C. 1886-8, 1895-7. S. 1893-5. V.-P. 1898—1900.)

1895 Box, Charles R., M.D., 2, Devonshire place, Portland Place, W.

1892 Boyce, Rubert William, M.S., F.R.S., Thompson Yates Laboratories, Liverpool University, Liverpool.

1904 Boycott, Arthur Pagin, B.Sc., M.B , B.Ch., Guy's Hospital, S.E.

1882 Boyd, Stanley, B.S., 134, Harley street, W. (C. 1893-6. V.-P. 1897-9.)

1889 Bradford, John Rose, M.D., F.R.S. 8, Manchester square, W. (C. 1897—1900. C. Com. Sect. C, 1902-5. S. 1900-2.)

1880 Bramwell, Byrom, M.D., 23, Drumsheugh Gardens West, Edinburgh.

1904 Branson, William P. S., M.B., 59, Gordon square, W.C.

1889 Bredin, J. Noble, The Vines, Sutton Valence, Maidstone.

1902 Brewerton, Elmore W., 84, Wimpole street, W.

1877 Bridges, Robert, M.B., M.A., Manor House, Yattendon, Berks.

1867 **Bridgewater**, Thomas, LL.D. Glas., M.B. Lond., Harrow-on-the-Hill, Middlesex.

1873 Briggs, Jacob Myers, M.D., Coeymans, New York, U.S.A.

1868 Bright, George Charles, M.D., Cannes, Alpes Maritimes, France.

1902 Brincker, John Augustus Herman, M.B., B.C., Borough Hospital, Waddon, Croydon.

1857 Briscoe, John, 5, Broad street, Oxford.

1904 Briscoe, John Charlton, M.B., 110, Harley street, W.

1885 Briscoe, John F., Westbrooke House, Alton, Hants.

1903 Broadbent, J. F. H , M.D., 35, Seymour street, W.

1860 **Broadbent**, Sir William Henry, Bart., K.C.V.O., M.D., F.R S., 84, Brook street, W. (C. 1871-3. V.P. 1882-4.)

1886 Brockatt, Andrew Alexander, M.D., Hazeldean, Malvern.

1884 Brodie, Charles Gordon, Fernhill, Wootton Bridge, Isle of Wight.

1899 Brodie, Thomas Grigor, M.D., F.R.S. (Hon. Secretary, Section C.), 4, Lancaster terrace, Regent's Park, N.W. (C. 1900—1901. S. Com. Sect. C, 1901—.)

1871 Brown, Frederick Gordon, 17, Finsbury circus, E.C.

1903 Browne, H. S. D., 78, High street, Winchester.

1877 Bruce, J. Mitchell, M.D., 23, Harley street, W.

1902 Bruce, Samuel Noble, 15, Queensborough terrace, W.

1890 Brunton, Sir T. Lauder, M.D., D.Sc., LL.D., F.R.S., 10, Stratford place, W.

1855 **Bryant**, Thomas, M.Ch. (Trustee), 42, Norfolk square, W. (C. 1863-6. V.-P. 1877-9.)

1894 Buchanan, George Seaton, M.D., 9, Hammersmith terrace, W.

1890 Buckland, Francis O., M.A., M.B., C.M., Brockenhurst, Hants.

1899 Bulloch, William, M.D., M.B., C.M. (Hon. Secretary, Sect. B), 66, Holland road, Kensington, W. (C. Com. Sect. B, 1901-3. S. Com. Sect. B, 1903—.)

1891 Burghard, Frédéric François, M.D., M.S., 86, Harley street, W.

1880 Burton, Samuel Herbert, M.B., 50, St. Giles' street, Norwich.

1900 Busch, Joseph Paul-Zum, M.D., Chiswell House, 133, Finsbury Pavement, E.C.

1903 Bushnell, Frank George, M.D., Sussex County Hospital, Brighton.

*Elected*

1872 **BUTLIN**, Henry Trentham, D.C.L., 82, Harley street, W. (M.G.C. 1875-86. C. 1876-8, 1887-9. S. 1884-6. V.-P. 1891-2. P. 1895-7.)

1883 **BUXTON**, Dudley W., M.D., 82, Mortimer street, W.

1903 Buzzard, Edward Farquhar, M.D., 33, Harley street, W. (C. Com. Sect. A, 1906—.)

1856 **BUZZARD**, Thomas, M.D., 74, Grosvenor street, W. (C. 1869-70. V.-P. 1881-3.)

1901 Caddy, Adrian, M.B., 2/2, Harington street, Calcutta.

1899 Caddy, Arnold, 2/2, Harington street, Calcutta.

1893 Caley, Henry Albert, M.D., 24, Upper Berkeley street, W.

1897 Calvert, James, M.D., 113, Harley street, W.

1905 Cammidge, Percy John, M.B., 2, Beaumont street, Portland place, W.

1892 Campbell, Henry Johnstone, M.D., 36, Manningham lane, Bradford.

1905 Candler, John Pycock, M.B., B.C., 65, Shepherd's Bush road, W.

1897 **Carwardine**, Thomas, M.S., 16, Victoria square, Clifton, Bristol.

1877 Casson, John Hornsey, H.B.M. Legation, Teheran, Persia.

1864 Cay, Charles Vidler, Deputy Surgeon General. Address uncommunicated.

1869 Chaffers, Edward, Abbotsrood, Milnthorpe road, Eastbourne.

1884 Chavasse, Sir Thomas Frederick, M.D., C.M., 22, Temple row, Birmingham.

1901 Cheatle, G. Lenthal, 117, Harley Street, W.

1879 Cheyne, William Watson, C.B., M.B., C.M., F.R.S., 75, Harley street, W. (C. 1885-7. M.G.C. 1890-6. V.-P. 1892-3. P. 1899—1902.)

1873 Chisholm, Edwin, M.D., 44, Rosslyn gardens, Darlinghurst, near Sydney, New South Wales [care of Messrs. Dawson, 121, Cannon street, E.C.].

1865 **CHURCH**, Sir William Selby, Bart., K.C.B., 130, Harley street, W. (M.G.C. 1869-74. C. 1871-3. V.-P. 1894-6.)

1868 **CHURCHILL**, Frederick, M.D., 4, Cranley gardens, Queen's gate, S.W.

1893 Churton, Thomas, M.D., 35, Park square, Leeds.

1861 **CLAPTON**, Edward, M.D., Towercroft, 41, Eltham road, Lee, S.E.

1872 Clark, Andrew, 71, Harley street, W.

1886 Clark, Francis William, M.B., Victoria, Hong Kong.

1885 Clarke, John Michell, M.D., 28, Pembroke road, Clifton, Bristol.

1881 Clarke, W. Bruce, M.B., 51, Harley street, W. (C. 1892-4.)

1904 Cleland, John Burton, M.D., Central Board of Health, Perth, W. Australia.

1899 Cleveland, Arthur John, M.D., 45, Shooter's Hill road, Blackheath Park, S.E.

1875 **CLUTTON**, Henry Hugh, M.A. (Treasurer), 2, Portland place, W. (C. 1881-6. M.G.C. 1889-94. V.-P. 1892-3. T. 1906—.)

1865 **Coates**, Charles, M.D., 10, Circus, Bath.

1892 Cole, Robert Henry, M.D., Moorcroft, Hillingdon, Uxbridge.

1886 Collier, William, M.D., High street, Oxford.

1888 Collins, Sir William Job, M.P., M.D., M.S., 1, Albert terrace, Regent's park, N.W.

*Elected*

1888 COLMAN, WALTER STACY, M.D., 9, Wimpole street, W.

1882 COLQUHOUN, DANIEL, M.D., Dunedin, New Zealand.

1905 COLWELL, HECTOR ALFRED, M.B., 55, Bridge road, Hornsey, N.

1896 CONNELL, W. T., M.D., Kingston, Canada.

1891 COOK, HERBERT G. GRAHAM, M.D., 22, Newport road, Cardiff.

1858 COOKE, R. T. E. BARRINGTON, 15, St. Nicholas cliff, Scarborough, Yorkshire.

1866 COOMBS, ROWLAND HILL, M.D., Mill street, Bedford.

1892 COOPER, C. DUDLEY [address uncommunicated].

1903 COOPER, PERCY ROBERT, M.D., B.Sc., Glenthorne, The Downs, Bowdon, Cheshire.

1900 CORNER, EDRED MOSS, M.B., 37, Harley street, W.

1899 CORNER, HARRY, M.D., Brook House, Southgate, N.

1861 **COUPER**, JOHN, 80, Grosvenor street, W. (C. 1870-2.)

1873 **COUPLAND**, SIDNEY, M.D., 16, Queen Anne street, W. (M.G.C. 1882-6. C. 1878-81, 1889-91. S. 1886-8. V.-P. 1892-3. T. 1894—1903.)

1904 COVENTON, CHARLES ARTHUR, 111, Woodstock road, Oxford.

1884 CRICHTON, GEORGE, M.D., 114, Lexham gardens, Kensington, W.

1873 CRIPPS, WILLIAM HARRISON, 2, Stratford place, W. (C. 1883-5. V.-P. 1893-4.)

1877 **CROCKER**, HENRY RADCLIFFE, M.D., 121, Harley street, W. (C. 1887-9. V.-P. 1897-9.)

1886 CROOKSHANK, EDGAR, M.B., Saint Hill, East Grinstead, Sussex. (C. 1890-3. V.-P., 1900-2.)

1875 CROSS, FRANCIS RICHARDSON, 5, The Mall, Clifton, Bristol.

1889 CUFF, ROBERT, M.B., 40, Filey road, Scarborough.

1871 CUMBERBATCH, A. ELKIN, 11, Park crescent, Portland place, W.

1893 CURTIS, HENRY JONES, M.D., 58, Harley Street, W.

1884 DAKIN, W. RADFORD, M.D., B.S., 8A, Grosvenor street, Grosvenor square, W.

1883 DALTON, NORMAN, M.D., 4, Mansfield street, W. (C. Com. Sect. A, 1901-3.)

1883 DAVIS, EDWIN HARRY, West Hartlepool.

1859 **Davis**, FRANCIS WILLIAM, R.N.

1879 DAVY, HENRY, M.D., 29, Southernhay, Exeter.

1894 DAWSON, BERTRAND, M.D., 32, Wimpole street, W.

1899 DEAN, GEORGE, M.D., The Lister Institute of Preventive Medicine, Queensberry Lodge, Elstree, Herts. (C. Com. Sect. B, 1905—.)

1889 DEAN, HENRY PERCY, M.B., M.S., 69, Harley street, W. (C. 1900—1901.)

1905 DEAN, HENRY RAY, M.B., B.Ch., 53, Elm Park gardens, S.W.

1899 DE CHAZAL, EDMOND LUCIEN, M.D., Port Louis, Mauritius.

1887 DELÉPINE, SHERIDAN, M.B., C.M., The Owens College, Manchester. (C. 1899—1901.)

1880 DENT, CLINTON T., 61, Brook street, W.

1871 DICKINSON, EDWARD HARRIMAN, M.A., M.D. Address uncommunicated.

*Elected*

1858 **DICKINSON**, WILLIAM HOWSHIP, M.D., 10, Stanhope place, Marble arch, W. (C. 1866-8. S. 1869-71. V.-P. 1872-4. P. 1889-90.)

1900 DIXON, W. E., M.D., Hazelwood, Netherby road, Honor Oak, S.E., and Pathological Laboratory, Cambridge.

1872 DIVER, EBENEZER, M.D., 95, London road, Portsmouth.

1872 DORAN, ALBAN HENRY GRIFFITHS, 9, Granville place, W. (C. 1882-4. V.-P. 1894-6.)

1893 DOWSON, WALTER, M.D., Newcome, Stanley road, Sutton, Surrey.

1877 DRAKE-BROCKMAN, EDWARD F., 14, Welbeck street, W.

1880 DRESCHFELD, JULIUS, M.D., 3, St. Peter's square, Manchester. (C. 1896-9.)

1893 DRYSDALE, JOHN HANNAH, M.D., 11, Devonshire place, W. (C. Com. Sect. A, 1904—.)

1865 **DUCKWORTH**, Sir DYCE, M.D., LL.D., 28, Grosvenor place, S.W (C. 1877.)

1902 DUDGEON, L. S., 6, Powis gardens, Bayswater, W.

1871 DUKES, CLEMENT, M.D., B.S., Sunnyside, Rugby.

1877 DUNBAR, J. J. MACWHIRTER, M.D., Hedingham House, Clapham common, S.W.

1889 DUNCAN, JOHN, M.D., St. Petersburg.

1884 DUNN, LOUIS ALBERT, M.B., M.S., 51, Devonshire street, Portland place, W.

1879 DURHAM, FREDERIC, M.B., 52, Brook street, W.

1899 EASTES, GEORGE LESLIE, M.B., B.Sc., 35, Gloucester terrace, W.

1901 EASTWOOD, A., M.D., Tuberculosis Commission, Stansted, Essex.

1893 ECCLES, WILLIAM MCADAM, M.S., 124, Harley street, W.

1892 EDDOWES, ALFRED, M.D., 28, Wimpole street, W.

1904 EDMUNDS, ARTHUR, M.S., 20, Upper Wimpole street, W.

1880 **EDMUNDS**, WALTER, M.C., 2, Devonshire place, Portland place, W. (C. 1892-4. C. Com. Sect. C, 1901-2.)

1889 ELAM, WILLIAM HENRY, New Barnet, Herts.

1883 ELDER, GEORGE, M.D., 17, Regent street, Nottingham.

1867 ELLIS, JAMES, M.D., Coburg street, Fratton, Portsmouth, and California.

1902 EMANUEL, JOSEPH GEORGE, M.B., B.S., B.Sc., 47, Newhall street, Birmingham.

1902 EMERY, WALTER D'ESTE, M.D., 141, Harley street, W. (C. Com. Sect. B. 1906—.)

1863 ENGELMANN, GEORGE JULIUS, M.D., A.M., 336, Beacon street, Boston, Mass., U.S.A.

1879 EVE, FREDERIC S., 125, Harley street, W. (M.G.C. 1884-94. C. 1885-7. V.-P. 1895-7.)

1876 EWART, JAMES COSSAR, M.B., C.M., F.R.S., School of Medicine, Edinburgh.

1877 **EWART**, WILLIAM, M.D., 33, Curzon street, W. (C. 1889-91.)

1859 **Ewens**, JOHN, 17, Redland Grove, Bristol.

1887 EYLES, CHARLES HENRY, Gold Coast Colony.

*Elected*

1897 EYRE, JOHN W. H., M.D., The Bacteriological Laboratory, Guy's Hospital, S.E. (C. Com. Sect. B, 1904—6.)

1889 FAIRBANK, FREDERICK ROYSTON, M.D., Hillside, Westcott, Dorking.

1894 FAWCETT, JOHN, M.D., 66, Wimpole street, W. (C. Com. Sect. A, 1902-5.)

1872 FENN, EDWARD L., M.D., Nayland, Colchester.

1902 FENNELL, CHARLES HENRY, M.A., M.B., County Asylum, Hellingly, Sussex.

1872 FENWICK, JOHN C. J., M.D., Long Framlington, Morpeth.

1892 FENWICK, W. SOLTAU, M.D., 29, Harley street, W.

1885 FÉRÉ, CHARLES, M.D., Médecin de Bicêtre; 22, Avenue Bugeaud, Paris.

1906 FIELD, FRANCIS EDWIN, M.B., Ch.B., Leavesden Asylum, King's Langley, Herts.

1904 FIELDING-OULD, ROBERT, M.D., B.Ch., 94, Mount street, Berkeley square, W.

1897 FISHER, THEODORE, M.D., 25, Pembroke road, Clifton, Bristol.

1893 FLETCHER, H. MORLEY, M.A., M.D., B.C., 98, Harley street, W. (C. Com. Sect. A, 1903—6. S. Sect. A, 1901-3.)

1904 FORBES, JAMES GRAHAM, M.D., 1, Duke street, Manchester square, W.

1866 **Foster**, Sir BALTHAZAR WALTER, M.D., M.P., 30, Grosvenor road, Westminster.

1891 FOULERTON, ALEXANDER GRANT RUSSELL, Rhynie, Hayward's Heath, Sussex. (C. 1900—1901. C. Com. Sect. B, 1903—6. S. Sect. B, 1901-3.)

1880 FOWLER, JAMES KINGSTON, M.A., M.D., 35, Clarges street, W. (C. 1887-8.)

1878 FOX, THOMAS COLCOTT, B.A., M.B., 14, Harley street, W. (C. 1892-4.)

1902 FREMLIN, H. STUART, Government Lymph Laboratory, Chelsea Bridge, S.W.

1896 FREYBERGER, LUDWIG, M.D., 41, Regent's park road, N.W. (C. Com. Sect. A, 1902-3.)

1891 FRIPP, Sir ALFRED DOWNING, C.B., M.V.O., M.S., 19, Portland place, W.

1864 FRODSHAM, JOHN MILL, M.D., Streatham, S.W.

1899 FÜRTH, KARL, M.D., 39, Harley street, W.

1894 FURNIVALL, PERCY, 28, Weymouth street, Portland place, W.

1893 FYFFE, WILLIAM KINGTON, M.B., 1, Boullcott street, Wellington, New Zealand.

1880 GABBETT, HENRY SINGER, M.D., 8, Chiswick place, Eastbourne.

1858 **Gairdner**, Sir WILLIAM TENNANT, K.C.B., M.D., LL.D.Edin., F.R.S., 32, George square, Edinburgh. (V.-P. 1891-2.)

1890 GALLOWAY, JAMES, M.A., M.D., 54, Harley street, W. (C. 1899-1902. Com. Sect. A, 1901-2.)

1870 GALTON, JOHN H., M.D., Sylvan road, Upper Norwood, S.E.

1846 **GARROD**, Sir ALFRED BARING, M.D., F.R.S., 10, Harley street, W. (C. 1851. V.-P. 1863-5.)

*Elected*

1892 GARROD, ARCHIBALD EDWARD, M.D. (HON. SECRETARY, SECT. D), 9, Chandos street, Cavendish square, W. (C. 1898—1901. S. Sect. D, 1901—.)

1879 GARSTANG, THOMAS WALTER HARROPP, Englefield, Delamer road, Bowdon, Cheshire.

1872 GARTON, WILLIAM, M.D., Inglewood, Aughton, near Ormskirk, Lancashire.

1902 GASK, G. E., M.B., The Warden's House, St. Bartholomew's Hospital, E.C.

1880 GIBBES, HENEAGE, M.B., University of Michigan, Ann Arbor, Michigan, U.S.A.

1853 **GIBBON**, SEPTIMUS, M.D., 39, Oxford terrace, Hyde park, W.

1878 GIBBONS, ROBERT A., M.D., 29, Cadogan place, S.W.

1906 GIBSON, A. E., M.B., Pathological Department, University Museum, Oxford.

1876 GILL, JOHN, M.D., 30, West mall, Clifton, Bristol.

1881 GLYNN, THOMAS ROBINSON, M.D., 62, Rodney street, Liverpool.

1898 GOADBY, KENNETH WELDON, 21, New Cavendish street, Portland place, W. (C. Com. Sect. B, 1905—.)

1873 GODLEE, RICKMAN JOHN, M.B., M.S., 19, Wimpole street, W. (M.G.C. 1875-84. C. 1877-80, 1891-2. S. 1887-9. V.-P. 1893-4, 1902-5. Chairman, Sect. A.)

1878 **GOLDING-BIRD**, CUTHBERT H., M.B., B.S., 12, Queen Anne street, W. (C. 1885-7. V.-P. 1894-6.)

1902 GOODBODY, FRANCIS WOODCOCK, M.D., 6, Chandos street, W.

1871 GOODHART, JAMES FREDERIC, M.D., 25, Portland place, W. (M.G.C. 1874-86. C. 1876-8, 1886-8. S. 1883-5. V.-P. 1892-3.)

1894 GOSSAGE, ALFRED MILNE, M.B., B.Ch., 54, Upper Berkeley street, W.

1875 GOULD, ALFRED PEARCE, M.S., 10, Queen Anne street, W. (C. 1883-5. V.-P. 1898-1900.)

1870 GOWERS, Sir WILLIAM, M.D., F.R.S., 50, Queen Anne street, W. (C. 1878-9. V.P. 1896-7.)

1888 GRANT, J. DUNDAS, M.A., M.D., C.M., 18, Cavendish square, W.

1905 GRAY, HARRY TYRRELL, 48, Pembroke square, W.

1900 GREEN, ALAN B., M.A., M.D., B.C., Lister Institute of Preventive Medicine, Queensberry Lodge, Elstree, Herts.

1895 GREEN, CHARLES DAVID, M.D., The Ferns, South street, Romford. (C. 1900-2. C. Com. Sect. A, 1901-2.)

1867 GREEN, T. HENRY, M.D., 74, Wimpole street, W. (M.G.C. 1869-83. C. 1871-3, 1878-9. S. 1875-6. V.-P. 1886-8.)

1873 GREENFIELD, WILLIAM SMITH, M.D., B.S., 7, Heriot row, Edinburgh. (M.G.C. 1874-81. C. 1877-80. V.-P. 1893-4.)

1886 GREVES, EDWIN HYLA, M.D., Rodney House, Suffolk road, Bournemouth.

1887 GRIFFITHS, JOSEPH, M.D., C.M., 63, Trumpington street, Cambridge.

1876 GRIFFITHS, THOMAS D., M.D., Hearne Lodge, Swansea.

1900 GRUBE, KARL, M.D., Neuenahr, Germany.

1899 GRUBER, R., M.D., 67, Wimpole street, W.

1905 GRÜNBAUM, ALBERT SIDNEY FRANKAU, M.D., 38, Clarendon road, Leeds.

*Elected*

1902 GRÜNBAUM, O. F. F., M.D., D.Sc., 34, Wimpole street, W. (C. Com. Sect. D. 1906—.)

1887 HABERSHON, SAMUEL HERBERT, M.D., 88, Harley street, W. (C. Com. Sect. A, 1902-4.)

1851 **HACON**, E. DENNIS, 269, Mare street, Hackney, N.E. (C. 1872.)

1892 HADLEY, WILFRED JAMES, M.D., 33, Queen Anne street, W.

1882 HAIG, ALEXANDER, M.D., 7, Brook street, W.

1899 HALL, ARTHUR J., M.B., 342, Glossop road, Sheffield.

1905 HALL, JOHN BASIL, M.B., B.C., 116, Manningham lane, Bradford.

1904 HALL, ISAAC WALKER, M.D., The Owens College, Manchester.

1901 HALLIBURTON, WILLIAM DOBINSON, M.D., F.R.S., Church Cottage, 17, Marylebone road, W. (V.-P., Chairman Sect. D., 1901-5.)

1894 HALLIDIE, ANDREW HALLIDIE SMITH, M.B., 50, Noord street, Johannesburg.

1886 HAMILTON, DAVID JAMES, M.B., 41, Queen's road, Aberdeen.

1890 HANDFIELD-JONES, MONTAGU, M.D., 35, Cavendish square, W.

1886 HANDFORD, HENRY, M.D., Elmfield, Southwell.

1902 HANDLEY, WILLIAM SAMPSON, M.S., M.D., 77, Wimpole street, W.

1891 HANKIN, E. H., Agra, India.

1882 HARBINSON, ALEXANDER, M.D., County Lunatic Asylum, Lancaster.

1893 **HARLEY**, VAUGHAN, M.D., 25, Harley street, W. (C. Com. Sect. D, 1901—6.)

1901 HARMER, W. D., 45, Weymouth street, W.

1896 HARTLEY, PERCIVAL HORTON-SMITH, M.V.O., M.D., B.C., 19, Devonshire street, W.

1905 HARNETT, WALTER SIDWELL, M.B., B.C., St. Thomas's Hospital, S E.

1891 HASLAM, WILLIAM F., 8, Vicarage road, Edgbaston, Birmingham.

1904 HAWES, COLIN SADLER, Albany General Hospital, Grahamstown, South Africa.

1899 HAWKES, CLAUDE SOMERVILLE, Glencairn, Wickham terrace, Brisbane, Queensland, Australia.

1886 HAWKINS, FRANCIS HENRY, M.D., 73, London street, Reading.

1890 HAWKINS, HERBERT PENNELL, M.D., 56, Portland place, W. (C. 1898—1901.)

1900 HEATON, CHARLES, Westgate-on-Sea, Thanet, Kent.

1892 HEATON, GEORGE, M.B., B.Ch., 47, Newhall street, Birmingham.

1881 HEBB, RICHARD G., M.A., M.D., 50, Ridgmount gardens, Gower street, W.C. (M.G.C. 1891—1900. C. 1891-3. 1898—1901. S. 1896-7.)

1884 HEBBERT, CHARLES ALFRED, care of C. Baylor, 7, Water street, Boston, U.S.A.

1901 HÉDIN, SVEN GUSTAV, M.D., Lister Institute of Preventive Medicine, Chelsea bridge, S.W. (C. Com. Sect. D, 1901-4.)

1879 HENDERSON, GEORGE COURTENAY, M.D., Kingston, Jamaica, West Indies.

1869 HENSLEY, PHILIP J., M.D., Snaith Cottage, Surbiton Hill, Surrey.

1884 HERRINGHAM, WILMOT PARKER, M.D., 40, Wimpole street, W. (C. 1894-7. V.-P., Chairman, Sect. A, 1906—.)

1892 HEWLETT, RICHARD TANNER, M.D., Bacteriological Laboratory, King's College, Strand, W.C. (C. Com. Sect. B, 1902—.)

*Elected*

1897 HICHENS, PEVERELL S., M.B., B.Ch., 45, Sheep street, Northampton.
1900 HILLIER, WILLIAM THOMAS, Rougemont, Beaconsfield road, St. Albans.
1903 HOBDAY, F., F.R.C.V.S., 10, Silver street, Kensington, W.
1880 HOBSON, JOHN MORRISON, M.D., Glendalough, Morland road, Croydon.
1854 **HOLMES**, TIMOTHY, 6, Sussex place, Hyde park, W. (C. 1862-3. S. 1864-7. C. 1868. V.-P. 1869-71.)
1878 HOOD, DONALD WILLIAM CHARLES, C.V.O., M.D., 43, Green street, Park lane, W.
1864 HOOD, WHARTON P., M.D., 11, Seymour street, W.
1903 HOPEWELL-SMITH, ARTHUR, 37, Park street, Grosvenor square, W.
1895 HOPKINS, FREDERICK GOWLAND, M.B., F.R.S., New Museums, Cambridge. (C. 1899—1905. Com. Sect. D, 1901-5. V.P., Chairman Sect. D, 1905—.)
1900 HORDER, THOMAS J., M.D., B.Sc., 141, Harley street, W. (C. Com. Sect. B, 1906—.)
1897 HORNE, W. JOBSON, M.D., 23, Weymouth street, W.
1883 HORSLEY, Sir VICTOR, M.B., B.S., F.R.S., 25, Cavendish square, W. (C. 1888-9. V.-P. 1900-1902.)
1880 **HOVELL**, T. MARK, 105, Harley street, W.
1893 HOWARD, ROBERT JARED BLISS, M.D., 31, Queen Anne street, W.
1856 **HUDSON**, JOHN, M.D., 11, Cork street, W.
1874 HUMPHREYS, HENRY, M.D., St. Mary Church road, Torquay.
1897 HUNT, E. L., c/o King, King, and Co., Bombay.
1897 HUNT, GEORGE B., M.D., 47, Albemarle crescent, Scarborough.
1888 HUNTER, WILLIAM, M.D., 103, Harley street, W. (C. 1897-1900.)
1852 **HUTCHINSON**, JONATHAN, F.R.S., 15, Cavendish square, W. (C. 1856-9. V.-P. 1872-3, 1881-3. P. 1879-80.)
1901 HUTCHISON, ROBERT, M.D., 22, Queen Anne street, W. (C. Com. Sect. D, 1905—.)
1884 HUTTON, HENRY RICHMOND, M.B., 8A, St. John street, Manchester.

1880 INGRAM, ERNEST FORTESCUE, Newcastle, Natal, S. Africa.
1905 INMAN, ARTHUR CONYERS, M.B., B.C., St. Thomas's Hospital, S.E.

1886 JACKSON, ARTHUR MOLYNEUX, M.D., Kent County Asylum, Barming Heath, Maidstone.
1865 JACKSON, J. HUGHLINGS, M.D., F.R.S., 3, Manchester square, W. (C. 1872-3. V.-P. 1888-9.)
1875 JALLAND, WILLIAM HAMERTON, St. Leonard's House, Museum street, York.
1897 JAMES, GEORGE T. B., Carlisle mansions, Victoria street, S.W.
1888 JAMES, JAMES THOMAS, M.D., 108, Harley street, W.
1853 **Jardine**, JOHN LEE, Grandon Lodge, Holmwood, Surrey.
1904 JENNINGS, JOHN FREDERICK, M.B., B.S., St. Bartholomew's Hospital, E.C.
1881 JENNINGS, WILLIAM OSCAR, M.D., 74, Avenue Marceau, Paris.
1878 JOHNSON, ARTHUR JUKES, Yorkville, Ontario, Canada.
1876 JOHNSON, CHARLES HENRY, Winton House, Basingstoke, Hants.
1901 JOHNSON, EDWARD ANGAS, M.B., B.S., 50, Franklin street, Adelaide, South Australia.

*Elected*

1888 JOHNSON, RAYMOND, M.B., B.S., 11, Wimpole street, Cavendish square, W. (C. 1896-9.)

1899 JONAS, HERBERT C., M.D., Bear street, Barnstaple.

1853 **JONES**, SYDNEY, M.B., 8A, New Cavendish street, W. (C. 1864-6. V.-P. 1886-7.)

1888 JONES, TALFOURD, M.B., St. Davids, Pembury, Tunbridge Wells.

1862 **JONES**, THOMAS RIDGE, M.D., 4, Chesham place, S.W. (C. 1882-4.

1898 KEEP, ARTHUR CORRIE, M.D., M.C., 14, Gloucester place, W.

1897 KELLY, CHARLES E. M., M.D., Witney, Oxon.

1859 KIALLMARK, HENRY WALTER, 5, Pembridge gardens, W. (C. 1875-6.)

1882 KIDD, PERCY, M.D., 60, Brook street, W. (C. 1889-91.)

1901 KLEIN, EDWARD EMANUEL, M.D., F.R.S., Harewood, Riverdale gardens, Twickenham Park, Twickenham. (V.-P., Chairman, Sect. B, 1901-5.)

1903 LAKIN, CHARLES ERNEST, M.D., Middlesex Hospital, W.

1878 LANCEREAUX, ETIENNE, M.D., 44, Rue de la Bienfaisance, Paris.

1882 LANE, WILLIAM ARBUTHNOT, M.B., M.S., 21, Cavendish square, W. (C. 1891-3.)

1904 LANGMEAD, FREDERICK, M.D., 74, Oxford terrace, Hyde park, W.

1869 LARCHER, O., M.D.Par., 97, Rue de Passy, Paris. [M. Kliensieck, Libraire, Rue de Lille 11, Paris, per Messrs. Longmans.]

1884 LARDER, HERBERT, Whitechapel Infirmary, Vallance road, N.E.

1897 LATHAM, ARTHUR C., M.D., 38, Portland place, W.

1873 LATHAM, PETER WALLWORK, M.D., 17, Trumpington street, Cambridge.

1853 LAWRENCE, HENRY JOHN HUGHES, Picton House, Llandowror, St. Clears. (C. 1873-5.)

1892 LAWRENCE, THOMAS WILLIAM PELHAM, M.B., 12, North hill, Highgate, N. (C. Com. Sect. A, 1901-3.)

1893 LAWSON, ARNOLD, M.D., 12, Harley street, W.

1879 LAYCOCK, GEORGE LOCKWOOD, M.B., Melbourne, Victoria, Australia.

1891 LAZARUS-BARLOW, WALTER SYDNEY, M.D., Fernholme, Woodside Park, N. Finchley, N. (C. Com. Sect. C, 1901-4.)

1904 LEATHEM, ALFRED NEWMAN, Gwydor Cottage, Elmer's end, Beckenham.

1901 LEATHES, JOHN BERESFORD, M.B., 89, Albert Bridge road, Battersea park, S.W. (C. Com. Sect. D, 1904—.)

1875 LEDIARD, HENRY AMBROSE, M.D., 35, Lowther street, Carlisle. (C. 1897-1900.)

1906 LEDINGHAM, J. C. G., London Hospital Medical College, London Hospital, E.

1877 **LEES**, DAVID B., M.D., 22, Weymouth street, W. (C. 1890-2.)

1867 LEES, JOSEPH, M.D., 21, Brixton road, S.W.

1877 LEESON, JOHN RUDD, M.D., C.M., 6, Clifden road, Twickenham.

1868 LEGG, JOHN WICKHAM, M.D. (Travelling.) (C. 1874-5.)

1902 LEGG, THOMAS PERCY, M.B., 141, Harley street, W.

1892 LEITH, ROBERT FRASER CALDIE, M.B., C.M., B.Sc.

1892 **Leudet**, ROBERT, 72, Rue de Bellechasse, Paris, France.

1897 LISTER, THOMAS DAVID, 50, Brook street, W.

*Elected*

1895 LITTLE, ERNEST GRAHAM GORDON, M.D., 61, Wimpole street, W.
1889 LITTLE, JOHN FLETCHER, M.B., 125, Harley street, W.
1862 **LITTLE**, LOUIS S., 31, Grosvenor street, W.
1896 LITTLEWOOD, HARRY, 25, Park square, Leeds.
1863 **LIVEING**, ROBERT, M.D., 11, Manchester square, W. (C. 1876.)
1881 LUBBOCK, MONTAGU, M.D., 19, Grosvenor street, W.
1897 LUCAS, ALBERT, 9, Easy row, Birmingham.
1873 LUCAS, R. CLEMENT, M.B., B.S., 50, Wimpole street, W. (C. 1883-5.)
1887 LYON, THOMAS GLOVER, M.D., 1, Victoria square, S.W.

1904 McDONALD, STUART, 39, Thirlestane road, Edinburgh.
1893 McFADYEAN, Sir JOHN, M.B., Royal Veterinary College, Great College street, N.W. (C. 1899-1901. Com. Sect. B, 1901-4.)
1896 MACFADYEN, ALLAN, M.D., B.Sc., Lister Institute of Preventive Medicine, Chelsea gardens, S.W. (C. 1900-3. Com. Sect. B, 1901-3.)
1899 McGAVIN, LAWRIE H., 6, Mansfield street, Cavendish square, W.
1885 MACKENZIE, HECTOR WILLIAM GAVIN, M.A., M.D., 34, Upper Brook street, Grosvenor square, W. (C. 1895-7.)
1870 MACKENZIE, JOHN T., Bombay, India.
1878 MACKENZIE, Sir STEPHEN, M.D., Merrycourt, Great Bookham, Leatherhead, Surrey. (C. 1888-90.)
1902 MACKIE, FREDERIC PERCIVAL, Agents, *c/o* Grindlay, Groom and Co., Bombay.
1865 MACLAURIN, HENRY NORMAND, M.D., 187, Macquarie street, Sydney, New South Wales.
1896 McWEENEY, EDMOND JOSEPH, M.D., M.Ch., 84, St. Stephen's green, Dublin.
1885 MAGUIRE, ROBERT, M.D., 4, Seymour street, W.
1877 **MAKINS**, GEORGE HENRY, C.B., 47, Charles street, Berkeley square, W. (C. 1889-91. V.-P. 1899-1901.)
1887 MALCOLM, JOHN DAVID, M.B., C.M., 13, Portman street, W.
1892 MANN, HAROLD EDWARD, Alderney.
1890 MANSON, Sir PATRICK, K.C.M.G., M.D., C.M., F.R.S., 21, Queen Anne street, W. (C. 1900-1.)
1876 MAPLES, REGINALD, Kingsclere, near Newbury.
1904 MARRIAGE, HERBERT JAMES, M.B., B.S., 109, Harley street, W.
1868 MARSH, F. HOWARD, M.C., 14, Hertford street, Mayfair, W. (C 1876-7.) (V.-P 1889-90.)
1904 MARTIN, CHARLES J., M.B., D.Sc., F.R.S., Lister Institute of Preventive Medicine, Chelsea gardens, S.W. (C. Com. Sect. C, 1904—.)
1887 MARTIN, SIDNEY, M.D., B.S., F.R.S., 10, Mansfield street, W. (C. 1893-6. V.-P. 1900-1902.)
1889 MASON, DAVID JAMES, M.D., Rosemont, Maidenhead.
1898 MASTERMAN, ERNEST WILLIAM GURNEY, Surgeon, English Mission Hospital, Jerusalem, Syria.
1892 MASTERS, JOHN ALFRED, M.D., 94, Knightsbridge, S.W.
1884 MAUDSLEY, HENRY CARR, M.D., 11, Spring street, Melbourne, Victoria.
1902 MAVROGORDATO, ANTHONY, 8, Ladbroke gardens, W.

*Elected*

1897 MAXWELL, J. P., c/o E.P. Mission, Eng Chhun, Amoy, China.

1900 MAXWELL, JAMES LAIDLAW, M.D., E.P. Mission, Yai-nan-fu, Formosa, *viâ* Hong Kong.

1852 **MAY**, GEORGE, M.B., Reading.

1838 MAY, WILLIAM PAGE, M.D., B.Sc., 9, Manchester square, W., and Helouan, near Cairo, Egypt (November to April).

1881 MAYLARD, ALFRED ERNEST, M.B., 4, Berkeley terrace, Glasgow.

1874 MEREDITH, WILLIAM APPLETON, C.M., 21, Manchester square, W.

1894 MICHELS, ERNST, M.D., 48, Finsbury square, E.C.

1900 MILBURN, LESLIE, Kenley, Beverley gardens, Cullercoats, Northumberland.

1901 MOORE, ALFRED, Reculver Villa, Cheam road, Sutton, Surrey.

1899 MOORE, FREDERICK CRAVEN, M.D., The Priory, Ardwick Green, Manchester.

1879 MOORE, NORMAN, M.D., 94, Gloucester place, Portman square, W. (C. 1885-7. M.G.C. 1889-1900. V.-P. 1895-7.)

1875 MORGAN, JOHN H., C.V.O., 68, Grosvenor street, W. (C. 1886-8.)

1874 MORISON, ALEXANDER, M.D., C.M., 14, Upper Berkeley street, W.

1869 **MORRIS**, HENRY, M.A., M.B. (TRUSTEE), 8, Cavendish square, W. (C. 1877-9, 1884-6. S. 1881-3. V.-P. 1888-9.)

1879 MORRIS, MALCOLM ALEXANDER, 8, Harley street, W.

1894 MORRICE, GEORGE GAVIN, M.D., Holy Trinity Vicarage, Weymouth.

1891 MORTON, CHARLES A., 14, Vyvyan terrace, Clifton, Bristol.

1884 MOTT, FREDERICK WALKER, M.D., F.R.S., 25, Nottingham place, W. (C. 1891-3. V.-P. 1899-1901.)

1900 MUIR, ROBERT, M.D., 4, Alfred terrace, Glasgow.

1893 MUMMERY, JOHN HOWARD, 10, Cavendish place, W.

1899 MURRAY, GEORGE R., M.D., 11, Ellison place, Newcastle-on-Tyne.

1885 MURRAY, HUBERT MONTAGUE, M.D., 25, Manchester square, W. (C. 1896-9.)

1894 MURRAY, JOHN, M.B., B.Ch., 110, Harley street, W.

1901 NABARRO, DAVID, M.D., B.Sc., D.P.H., 4, Albemarle mansions, Heath Drive, N.W. (C. Com. Sect. B, 1906—.)

1887 NASON, EDWARD NOEL, M.D., 80, Abbey street, Nuneaton.

1904 NEAVE, SHEFFIELD, Mill Green park, Ingatestone, Essex.

1875 NEWBY, CHARLES HENRY, St. Mary's, Broad Park avenue, Ilfracombe.

1902 NEWLAND, HENRY SIMPSON, M.B., Ch.B., North terrace, Adelaide, S. Australia.

1865 NEWMAN, WILLIAM, M.D., Stamford, Lincolnshire.

1895 NIAS, J. BALDWIN, M.D., 5, Rosary gardens, S. Kensington, S.W.

1868 NICHOLLS, JAMES, M.D., Trekenning House, St. Columb, Cornwall.

1876 NICHOLSON, FRANK, M.D., 29, Albion street, Hull.

1864 **NORTON**, ARTHUR T., C.B., Leyfields Wood, Ashampstead, Berks. (C. 1877-9.)

1883 NORVILL, FREDERIC HARVEY, M.B., Dibrooghur, India.

1880 O'CONNOR, BERNARD, M.D., 32, Old Buildings, Lincoln's Inn, W.C.

1873 O'FARRELL, Sir GEORGE PLUNKETT, M.D., 19, Fitzwilliam square, Dublin.

*Elected*

1894 OGLE, CYRIL, M.D., 96, Gloucester place, W. (C. 1899-1901.)
1888 OPENSHAW, THOMAS HORROCKS, C.M.G., M.S., 16, Wimpole street, W.
1892 ORD, WILLIAM WALLIS, M.D., The Hall, Salisbury.
1879 ORMEROD, JOSEPH A., M.D., 25, Upper Wimpole street, W. (C. 1887-9.)
1875 OSBORN, SAMUEL, Maisonnette, Datchet, Bucks.
1865 OWLES, JAMES ALLDEN, M.D., Hill View, Woking, Surrey.

1884 PAGET, STEPHEN, 70, Harley street, W. (C. 1894-7.)
1895 PAKES, WALTER CHARLES, Government Laboratory, Pretoria, South Africa. (C. Com. Sect. B, 1901-2.)
1897 PARFITT, CHARLES D., M.D., London, Canada.
1893 PARKER, ARTHUR PERCY, M.B., B.Ch., 2, Holywell, Oxford.
1874 PARKER, RUSHTON, M.B., B.S., 59, Rodney street, Liverpool.
1853 PARKINSON, GEORGE, Orchard Dene, Henley-on-Thames.
1901 PARSONS, JOHN HERBERT, M.B., B.S., B.Sc., 27, Wimpole street, W.
1882 PASTEUR, WILLIAM, M.D., 4, Chandos street, W. (C. 1893-6.)
1885 PAUL, FRANK THOMAS, 38, Rodney street, Liverpool.
1865 PAVY, FREDERICK WILLIAM, M.D., LL.D., F.R.S., 35, Grosvenor street, W. (C. 1872-4. V.-P. 1891-2. V.-P., Chairman Sect. C, 1901—. P. 1893-4.)
1868 PAYNE, JOSEPH FRANK, M.D. (TRUSTEE), Lyonsdown House, New Barnet, Herts. (M.G.C. 1872-85. C. 1873-5, 1883-5. S. 1880-2. V.-P. 1888-9. V.-P., Chairman Sect. A, 1901-2. P. 1897-8.)
1872 PEARCE, JOSEPH CHANING, M.D., C.M., Montague House, St. Lawrence-on-Sea, Kent.
1879 PEEL, ROBERT, 130, Collins street East, Melbourne, Victoria.
1899 PEMBREY, MARCUS SEYMOUR, M.D., B.Ch., Guy's Hospital, S.E. (C. Com. Sect. C, 1904—.)
1889 PENBERTHY, JOHN, Royal Veterinary College, Camden Town, N.W.
1884 PEPPER, AUGUSTUS JOSEPH, M.B., C.M., 13, Wimpole street, W.
1900 PERKINS, JOSEPH JOHN, M.B., 41, Wimpole street, Cavendish square, W.
1899 PERNET, GEORGE, 91, Harley street, W.
1888 PERRY, Sir EDWIN COOPER, M.D., Superintendent's House, Guy's Hospital, S.E.
1901 PETRIE, GEORGE FORD, M.D., *c/o* King, King, & Co., Bombay.
1902 PHEAR, ARTHUR G., M.D., 47, Weymouth street, W.
1878 PHILIPPS, SUTHERLAND REES, M.D., 4, The Beacon, Exmouth.
1878 PHILLIPS, JOHN WALTER, 30, Stanley street West, Melbourne, Victoria.
1893 PINKERTON, ROBERT A., M.A., M.D., 15, South Norwood hill, S.E.
1884 PITT, GEORGE NEWTON, M.D., 15, Portland place, W. (M.G.C. 1889-97. C. 1890-2, 1896-9. S. 1894-6. V.-P. 1899-1901.)
1876 PITTS, BERNARD, M.A., M.C., 109, Harley street, W. (C. 1888-90.)
1899 PLIMMER, HENRY GEORGE, 3, Hall road, N.W. (C. Com. Sect. B. 1901-3.)
1883 POLAND, JOHN, 2, Mansfield street, Cavendish square, W.
1882 POLLARD, BILTON, M.B., B.S., 24, Harley street, W. (C. 1895-7.)
1850 POLLOCK, JAMES EDWARD, M.D., 37, Collingham place, W. (C. 1862-4. V.-P. 1879-81.)

*Elected*

1879 **POTTER**, HENRY PERCY, M.D., St. Mary Abbotts Infirmary, Marloes road, Kensington, W.

1866 POWELL, Sir RICHARD DOUGLAS, Bart., K.C.V.O., M.D., P.R.C.P., 62, Wimpole street, W. (C. 1873-5, 1881-3. S. 1877-9. V.-P. 1887-8.)

1884 **POWER**, D'ARCY, M.A., M.B., 10A, Chandos street, W. (C. 1891-3. 1899-1902. Com. Sect. A, 1901-2. M.G.C. 1897-1900. S. 1897-9.)

1865 POWER, HENRY, Bagdale Hall, Whitby. (C. 1876-7.)

1900 POYNTON, FREDERICK JOHN, M.D., 1, Harley place, Harley street, W. (C. Com. Sect. A, 1905—.)

1887 PRATT, WILLIAM SUTTON, M.D., Penrhos House, Rugby.

1902 PRICE, F. W., M.B., 133, Harley street, W.

1884 PRICE, JOHN A. P., M.D., 124, Castle street, Reading.

1900 PRICE-JONES, CECIL, M.B., Beachcote, The Bungalow, Walmer Beach.

1888 PRIMROSE, ALEXANDER, M.B., C.M., 100, College street, Toronto, Canada.

1895 PURVIS, WILLIAM PRIOR, M.D., 2, Avenue place, Southampton.

1865 PYE-SMITH, PHILIP HENRY, M.D., F.R.S. (PRESIDENT), 48, Brook street, W. (C. 1874-7. V.-P. 1890-1. Chairman Sect. A, 1905—6. T. 1903—6.)

1897 RANKIN, GUTHRIE, M.D., 4, Chesham street, S.W.

1890 **Ransom**, WILLIAM BRAMWELL, M.D., The Pavement, Nottingham.

1891 RATCLIFFE, JOSEPH RILEY, M.B., C.M., Wake green, Moseley.

1887 RAVEN, THOMAS FRANCIS, Broadstairs, Kent.

1870 RAY, EDWARD REYNOLDS, 15A, Upper Brook street, W.

1875 REID, ROBERT WILLIAM, M.D., C.M., 8, Queen's gardens, Aberdeen,

1901 REID, ST. GEORGE CAULFIELD, Brigstock House, Thornton Heath, Surrey.

1906 REID, SIDNEY THOMAS, R.N., Royal Naval Hospital, Chatham.

1901 REISSMANN, CHARLES, M.B., St. Peter's, College Town, Adelaide, S. Australia.

1881 RENNER, WILLIAM, Wilberforce street, Free Town, Sierra Leone.

1893 RENNIE, GEORGE EDWARD, M.D., College street, Hyde park, Sydney, N.S.W.

1895 RITCHIE, JAMES, M.D., 28, Beaumont street, Oxford. (C. Com. Sect. B, 1903-5.)

1901 RIVIERE, CLIVE, M.D., 19, Devonshire street, W.

1865 **Roberts**, DAVID LLOYD, M.D., 11, St. John's street, Manchester.

1871 ROBERTS, FREDERICK THOMAS, M.D., 102, Harley street, W. (C. 1883-5.)

1878 ROBERTS, WILLIAM HOWLAND, M.D., Surgeon, Madras Army.

1883 ROBERTSON, ROBERT, M.D., The Bungalow, Ventnor, Isle of Wight.

1885 ROBINSON, ARTHUR HENRY, M.D., St. Mary's Infirmary, Highgate hill, N.

1882 ROBINSON, TOM, M.D., 9, Princes street, Cavendish square, W.

1904 ROBSON, A. W. MAYO, 8, Park crescent, Portland place, W.

1888 ROLLESTON, HUMPHRY DAVY, M.A., M.D. 55, Upper Brook street, Grosvenor square, W. (C. 1894-7. 1900-1902. Com. Sect. A, 1901-2. M.G.C. 1895-1900. S. 1898-1900.)

1904 ROSE, FRANK ATCHERLEY, M.B., 3, Upper Wimpole street, W.

*Elected*

1858 **ROSE**, HENRY COOPER, M.D., 16, Warwick road, Maida hill, N.W. (C. 1873-4.)

1906 ROSS, ERNEST ATHOLE, M.B., B.C., 54, Nevern square, S.W.

1875 ROSSITER, GEORGE FREDERICK, M.B., Cairo Lodge, Weston-super-Mare.

1877 **ROTH**, BERNARD, 38, Harley street, W., and Kingswood, Enfield.

1891 ROUILLARD, LAURENT ANTOINE JOHN, M.B., Durban, Natal.

1901 ROWLAND, SYDNEY, M.A., Lister Institute of Preventive Medicine, S.W.

1899 ROWLANDS, ROBERT P., 6, St. Thomas's street, London Bridge, S.E.

1891 RÜFFER, MARC ARMAND, M.D., The Quarantine Board, Alexandria.

1897 RUNDLE, HENRY, 13, Clarance parade, Southsea.

1900 RUSSELL, A. E., M.D., 9, Wimpole street, Cavendish square, W.

1895 RUSSELL, JAMES SAMUEL RISIEN, M.D., 44, Wimpole street, Cavendish square, W.

1891 RUSSELL, WILLIAM, M.D., 3, Walker street, Edinburgh.

1903 SALAMAN, REDCLIFFE N., M.B., Barley, Royston, Herts.

1902 SARGENT, PERCY WILLIAM GEORGE, M.B, B.C., 37, Harley street, W.

1886 SAUNDBY, ROBERT, M.D., 140B, Great Charles street, Birmingham.

1871 SAUNDERS, CHARLES EDWARD, M.D., Sussex County Lunatic Asylum, Hayward's Heath.

1901 SAUNDERS, E. Arthur, M.B., 49, Harley street, W.

1890 SAUNDERS, FREDERICK WILLIAM, M.B., B.C., Chieveley House, Newbury.

1873 SAVAGE, GEORGE HENRY, M.D., 26, Devonshire place, W. (C. 1881-3.)

1882 SAVILL, THOMAS DIXON, M.D., 60, Upper Berkeley street, W.

1902 SCHÖLBERG, H. A., M.B., University College of South Wales and Monmouthshire, Cardiff.

1891 SCHORSTEIN, GUSTAVE ISIDORE, M.B., B.Ch., 11, Portland place, W.

1901 SCOTT, Hon. G. H., M.B, B.C., Mertoun House, St. Boswells, N.B.

1902 SCOTT, S. G., M.A., M.B., Yorkshire College, Department of Medicine, Thoresby place, Leeds.

1899 SELIGMANN, CHARLES G., M.B., 15, York terrace, Regent's Park, N.W. (C. Com. Sect. A, 1905—.)

1903 SELOUS, C. F., M.B., St. Thomas's Hospital, Albert Embankment, S.E.

1877 SEMON, Sir FELIX, C.V.O., M.D., 39, Wimpole street, W. (C. 1885-7.)

1894 SEQUEIRA, JAMES HARRY, M.D., 63, Harley street, Cavendish square, W.

1872 SERGEANT, EDWARD, D.P.H., Lancashire County Council, Public Health Department, County Offices, Preston.

1876 SHARKEY, SEYMOUR J., M.D., 22, Harley street, W. (M.G.C. 1884-1895. C. 1884-6. V.-P. 1895-7.)

1880 SHATTOCK, SAMUEL G. (HON. GENERAL SECRETARY), 4, Crescent road, The Downs, Wimbledon, S.W. (M.G.C. 1884-1900. C. 1885-7. 1893-6. S. 1890-2, 1902—. V.-P. 1896-8. E. 1900—.)

1898 SHAW, HAROLD BATTY, M.D., 7, Devonshire street, W. (C. Com. Sect. A, 1903—6.)

1885 SHAW, LAURISTON ELGIE, M.D., 64, Harley street, W.

1886 **SHERRINGTON**, CHARLES SCOTT, M.D., F.R.S., University College, Liverpool. (C. 1894-7.)

1856 **SHILLITOE**, BUXTON, 2, Frederick's place, E.C.

*Elected*

1875 SIDDALL, JOSEPH BOWER, M.D., C.M., Conybeare, Northam, Bideford.

1901 SINGER, HAROLD DOUGLAS, M.D., McCagne Buildings, Omaha, Neb., U.S.A.

1892 SLATER, CHARLES, M.B., St. George's Hospital, S.W.

1887 SMALLPEICE, WILLIAM DONALD, 10, Chester square, S.W.

1887 **SMITH**, FREDERICK JOHN, M.D., 138, Harley street, W.

1894 SMITH, GUY BELLINGHAM, M.B., B.S., 24, St. Thomas's street, S.E.

1906 SMITH, J. HENDERSON, M.B., B.Ch., 225, Woodstock road, Oxford.

1900 SMITH, J. LORRAIN, M.D., The Victoria University of Manchester. (C. Com. Sect. C, 1905—.)

1873 SMITH, RICHARD T., M.D., 117, Haverstock hill, N.W.

1883 SMITH, ROBERT PERCY, M.D, 36, Queen Anne street, W.

1869 SMITH, ROBERT SHINGLETON, M.D., Deepholm, Clifton Park, Bristol.

1866 SMITH, WILLIAM, Melbourne, Australia.

1870 SNOW, WILLIAM VICARY, M.D., Richmond Gardens, Bournemouth.

1888 SOLLY, ERNEST, M.B., Strathlea, Harrogate, Yorks.

1887 SPENCER, WALTER GEORGE, M.S., 35, Brook street, W. (M.G.C. 1894-1900. C. 1896-9.)

1906 SPILSBURY, BERNARD H., M.B., B.Ch., 25, Cambridge Terrace, Hyd Park, W.

1899 SPRIGGS, EDMUND IVEN, M.D., 48, Bryanston Street, W.

1861 SQUIRE, ALEXANDER BALMANNO, M.B., 24, Weymouth street, W.

1901 STAINER, E., M.B., 60, Wimpole street, W.

1895 STARLING, ERNEST HENRY, M.D., F.R.S., 40, West end lane, N.W. (C. Com. Sect. C, 1901—.)

1896 STEPHENS, J. W. W., M.D., The Johnston Laboratory, The University, Liverpool.

1899 STEWARD, FRANCIS J., M.S., 125, Harley street, W.

1891 STILES, HAROLD JALLAND, M.B., C.M., 5, Castle terrace, Edinburgh.

1897 STILL, GEORGE F., M.D. (HON. SECRETARY, SECT. A), 114, Harley street, W. (C. Com. Sect. A, 1901-3. Sec. Sect. A, 1903—.)

1879 STIRLING, EDWARD CHARLES, C.M.G., M.D., F.R.S., Adelaide, South Australia [care of Messrs. Elder & Co., 7, St. Helen's place, E.C.].

1884 STONHAM, CHARLES, C.M.G., 4, Harley street, W. (C. 1893-6.)

1896 STRANGEWAYS, T. P., St. John's College, Cambridge.

1902 STRICKLAND-GOODALL, J., M.D., 30, Vanbrugh hill, Blackheath, S.E.

1903 STRONG, WALTER M., "Helstonleigh," Champion park, Denmark hill, S.E.

1875 STURGE, W. A., M.D., 29, Boulevard Dubouchage, Nice.

1867 SWAIN, WILLIAM PAUL, 17, The Crescent, Plymouth.

1881 SYMONDS, CHARTERS JAMES, M.S., 58, Portland place, W. (M.G.C. 1884-91. C. 1886-8. V.-P. 1899-1901.)

1886 TARGETT, JAMES HENRY, M.B., M.S., 19, Upper Wimpole street, W. (M.G.C. 1894-1900. C. 1894-5, 1897-1900. V.-P. 1900-1902. S. 1895-7.)

1870 TAY, WARREN, 4, Finsbury square, E.C. (C. 1881-2.)

1871 **TAYLOR**, FREDERICK, M.D., 20, Wimpole street, W. (M.G.C. 1879-89. C. 1879-81. V.-P. 1897-9.)

*Elected*

1885 TAYLOR, HENRY H., 10 Brunswick place, Hove, Sussex.
1892 TAYLOR, JAMES, M.D., 49, Welbeck street, W.
1902 THIELE, FRANCIS HUGO, M.D., 7, Hampstead lane, Highgate, N.
1891 THOMSON, HENRY ALEXIS, M.D., 39, Drumsheugh gardens, Edinburgh.
1884 THOMSON, JOHN, M.D., C.M., 14, Coates crescent, Edinburgh.
1901 THOMSON-WALKER, J. W., M.B., 30, Queen Anne street, W.
1893 **Thorburn**, WILLIAM, B.S., 2, St. Peter's square, and Rusholme Lodge, Rusholme, Manchester.
1872 THORNTON, WILLIAM PUGIN, 35, St. George's place, Canterbury.
1900 THURSFIELD, HUGH, M.D., 84, Wimpole street, W. (C. Com. Sect. A, 1905—.)
1880 TIRARD, NESTOR ISIDORE, M.D., 74, Harley street, W.
1884 TIVY, WILLIAM JAMES, 8, Lansdowne place, Clifton, Bristol.
1882 TOOTH, HOWARD HENRY, C.M.G., M.D., 34, Harley street, W. (C. 1892-4. M.G.C. 1895-1900.)
1886 TOTSUKA, KANKAI, Tokio, Japan.
1872 **TOWNSEND**, THOMAS SUTTON, 68, Queen's gate, S.W.
1899 TREDGOLD, ALFRED F., London County Asylum, Woodford Bridge, Essex.
1888 TREVELYAN, EDMOND F., M.D., 40, Park square, Leeds.
1902 TREVOR, ROBERT SALUSBURY, M.B., 21, Fitzgeorge avenue, West Kensington, W.
1851 TROTTER, JOHN W., 4, St. Peter's terrace, York. (C. 1865-9.)
1904 TROTTER, WILFRED BATTEN LEWIS, M.S., 13, Harley street, W.
1895 TROUTBECK, HENRY, M.B., B.C., 151, Ashley gardens, S.W.
1859 **TRUMAN**, EDWIN THOMAS, 23, Old Burlington street, W.
1888 TUBBY, ALFRED HERBERT, M.S., 68, Harley street, W.
1858 TUDOR, JOHN, Dorchester, Dorset.
1893 TURNEY, HORACE GEORGE, M.D., M.Ch., 68, Portland place, W.
1858 **TURTLE**, FREDERICK, M.D., Kirkmead, Woodford, Essex.
1880 TYSON, WILLIAM JOSEPH, M.D., 10, Langhorne gardens, Folkestone.

1867 VENNING, Sir EDGCOMBE, 30, Cadogan place, S.W.
1889 VOELCKER, ARTHUR FRANCIS, M.D., B.S., 101, Harley street, W. (C. 1895-7.)

1867 **WAGSTAFFE**, WILLIAM WARWICK, B.A., Purleigh, St. John's hill, Sevenoaks. (C. 1874, 1878-80. M.G.C. 1874-82. S. 1875-7.)
1885 WAKLEY, THOMAS, jun., 16, Hyde park gate, S.W.
1902 WALKER, E. W. AINLEY, M.D., University College, Oxford.
1893 WALKER, NORMAN PURVIS, M.D., 7, Manor place, Edinburgh.
1901 WALLACE, CUTHBERT SIDNEY, 26, Upper Wimpole street, W.
1881 WALLER, BRYAN CHARLES, M.D., Masongill House, Cowan bridge Kirkby-Lonsdale.
1890 WALLIS, FREDERICK CHARLES, M.B., B.C., 107, Harley street, W. (C. 1898-1901.)
1888 WALSHAM, HUGH, M.A., M.D., B.C., 114, Harley street, W.
1859 WALTERS, JOHN, M.B., Reigate, Surrey.
1892 WARD, ALLAN OGIER, M.D. Edin., 73, Cheapside, E.C.

*Elected*

1903 WARD, EDWARD, M.B., B.C., 30, Park square, Leeds.

1892 WARING, HOLBURT JACOB, M.B., M.S., 37, Wimpole street, W.

1891 WATERHOUSE, HERBERT FURNIVALL, M.D., C.M., 81, Wimpole street, W.

1903 WATERS, W. A. P., M.D., 99, Holywell, Oxford.

1890 WEBB, CHARLES FREKE, M.D., New street House, Basingstoke.

1894 **WEBER**, FREDERICK PARKES, M.D., 19, Harley street, W. (C. Com. Sect. A, 1906—.)

1858 **WEBER**, Sir HERMANN, M.D., 10, Grosvenor street, W. (C. 1867-70. V.-P. 1878-80.)

1864 WELCH, THOMAS DAVIES, M.D. (Travelling).

1894 WELLS, SYDNEY RUSSELL, M.D., 24, Somerset street, Portman square, W.

1892 WESBROOK, FRANK F., M.D., The University of Minnesota, Minneapolis, U.S.A.

1877 WEST, SAMUEL, M.D., 15, Wimpole street, W. (C.1884-6, 1891-3. S. 1889-90. V.-P. 1896-7.)

1891 WHEATON, SAMUEL WALTON, M.D., 10, Restall avenue, Streatham hill, S.W.

1869 WHIPPLE, JOHN H. C., M.D., Royal Army Medical Corps.

1877 WHITE, CHARLES HAYDON, 4, East Circus street, Park row, Nottingham.

1894 **WHITE**, CHARLES POWELL, M.B., Pathological Laboratory, Victoria University, Manchester. (C. Com. Sect. A, 1903-5.)

1891 WHITE, GILBERT B. MOWER, M.B., B.S., 112, Harley street, W.

1881 WHITE, WILLIAM HALE, M.D., 65, Harley street, W. (C. 1888-90.)

1886 WHITE, WILLIAM HENRY, M.D., 43, Weymouth street, W.

1868 **Whitehead**, WALTER, Birchfield, 235, Wilmslow road, Manchester.

1897 WHITFIELD, ARTHUR, M.D., 21, Bentinck street, Manchester square, W. (C. Com. Sect. A, 1905—.)

1869 WILKIN, JOHN F., M.D., M.C., Rose Ash Court, N Devon.

1871 WILKINSON, J. SEBASTIAN. Address uncommunicated.

1879 WILLCOCKS, FREDERICK, M.D., The Hawthorns, Burnham, Somerset.

1869 WILLIAMS, ALBERT, M.D. (Travelling).

1858 **Williams**, CHARLES, 48, Prince of Wales road, Norwich.

1866 WILLIAMS, CHARLES THEODORE, M.V.O., M.D., 2, Upper Brook street, W. (C. 1875-8.)

1881 WILLIAMS, DAWSON, M.D., B.S., 2, Agar street, Strand, W.C. (C. 1893-6.)

1881 WILLIAMS, W. ROGER, Beaufort House, Clifton Down, Clifton.

1900 WILLIAMSON, OLIVER K., M.B., B.C., 55, Upper Berkeley street, W.

1863 WILLIS, FRANCIS, M.D., Asheville, N. Carolina, U.S.A.

1889 WILSON, ALBERT, M.D., 1, Belsize park, N.W.

1888 WILSON, CLAUDE, M.D., C.M., Church road, Tunbridge Wells.

1859 WILSON, EDWARD THOMAS, M.B., Montpelier terrace, Cheltenham.

1891 WILSON, THEODORE STACEY, M.D., C.M., 27, Wheeley's road, Edgbaston, Birmingham.

1861 **Windsor**, THOMAS, Brownlow, Great Budworth, Northwich.

*Elected*

1874 WISEMAN, JOHN GREAVES, Stranraer, St. Peter's Road, St. Margaret's-on-Thames.

1883 WOODCOCK, JOHN ROSTRON, Darlington Court, North road, Bath.

1883 WOODHEAD, GERMAN SIMS, M.D., 6, Scrope terrace, Cambridge. (C. 1891-3. V.-P. 1898—1900. M.G.C. 1899—1900.)

1879 WOODWARD, G. P. M., M.D., Deputy Surgeon General; Sydney, New South Wales.

1884 WORTS, EDWIN, 6, Trinity street, Colchester.

1903 WRIGHT, Sir ALMROTH EDWARD, M.D., 7, Lower Seymour street, Portman square, W. (C. Com. Sect. B, 1903-5. V.-P., Chairman Sect. B, 1905—.)

1890 WYNNE, EDWARD T., M.B., Gladstone, Queensland.

1884 WYNTER, WALTER ESSEX, M.D., 27, Wimpole street, W.

1872 YOUNG, HENRY, M.B., Monte Video, South America.

1901 YOUNG, HENRY WILLIAM PENNEFATHER, "Dursley," Norbury, S.W.

# ANNUAL REPORT OF COUNCIL,

# 1905-6.

PRESENTED AT THE ANNUAL MEETING, MAY 29TH, 1906.

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YOUR Council have to report that during the present session twelve new members have been admitted to the Society, that twenty-three members have resigned, and that there have been eight losses by death.

The death-roll comprises: Dr. Lionel Smith Beale, Dr. Julian Evans, Sir Joseph Ewart, Mr. Christopher Heath, Mr. J. A. Kingdon, Dr. John Morton, Sir John Burdon Sanderson, Dr. H. M. Tuckwell.

The total number of members is now 661, of whom a certain number are, under the older regulations, non-resident.

Four Laboratory meetings have been held—viz. at University College; the Lister Institute, Chelsea; the Royal Army Medical College; and St. Bartholomew's Hospital.

To the directors of the Pathological Laboratories of these institutions the Council offers its best thanks.

A special meeting was held in June at the Asylum at Claybury, on Dr. F. W. Mott's invitation, to whom the Council likewise expresses its obligations and thanks.

In regard to the proposed Confederation of the London Medical Societies, the Council has to offer the following report:

Dr. A. E. Garrod is serving on behalf of the Society on the General Organising Committee, which is engaged in elaborating the details of the scheme.

An interview with the Organising Committee was held in

May, 1906, the delegates representing the Society being Dr. Garrod, and the general secretary.

In November, 1905, the Council made certain suggestions and stipulations with reference to the proposed Confederation. Most of these have been agreed to by the Organising Committee, others are yet undecided. This being the case, the Council has determined that the following resolution be put to the general meeting, May 29th, 1906, from the chair:

"That the Society is in favour of the proposal to amalgamate the Medical Societies of London, and is willing to co-operate in bringing about such amalgamation."[1]

The following are some of the chief results which will follow from the Confederation:

The Pathological Society will become the Pathological Section of the new Royal Academy of Medicine.

In the new Royal Academy of Medicine, a payment of one guinea year will entitle a member of the Pathological Society to be a member of the Pathological Section, and to receive a copy of all the work done in the section.

A subscription of three guineas will entitle a member to attend the meetings of all the sections, possibly some fifteen or more in number, and also to use the library, the basis of which library will be that of the present Royal Medical and Chirurgical Society.

The new Academy will publish monthly 'Proceedings' and annual 'Transactions.'

A member of the Pathological Section only will receive a monthly fasciculus containing the work done in his section, and a copy of whatever appears from the Pathological section in the 'Transactions.'

The editing of the whole of the 'Proceedings' and 'Transactions' will be in the hands of a General Editorial Committee on which the sections will be represented—whether all is not yet decided.

## Report of the Treasurer.

In placing the accounts of the Society before the meeting, the Treasurer reports that we had to use £200 of our savings in order to bring out the annual volume in the admirable style

[1] This resolution was adopted by the general meeting.

which has become characteristic of our Society. The decision of the Council was the best way of meeting the difficulty, and it was unanimous. We have paid our way, and the balance-sheet is satisfactory. I have sent out two sets of reminders addressed to members whose subscriptions were over-due, and the result has been most satisfactory.

Financially, we have passed through the trying period of uncertainty as to the future of this as of other medical societies in London, and we have good reason to believe that our amalgamation will be for our advantage, and will not be long delayed.

P. H. Pye-Smith.

# THE PATHOLOGICAL SOCIETY OF LONDON.

*Statement of Receipts and Payments from 14th May, 1905, to 26th May, 1906.*

| RECEIPTS. | £ | s. | d. |
|---|---|---|---|
| Petty Cash in hand, 13th May, 1905 | 6 | 10 | 10 |
| 348 Subscriptions at £1 1s. | 365 | 8 | 0 |
| 7 Entrance Fees at £1 1s. | 7 | 7 | 0 |
| Sale of 'Transactions' | 44 | 10 | 8 |
| 10 Fees for Agenda Notices at 2s. 6d. | 1 | 5 | 0 |
| *Dividends* on Consols | 20 | 5 | 8 |
| Sale of Consols | 200 | 11 | 6 |
| | £645 | 18 | 8 |

| PAYMENTS. | £ | s. | d. | £ | s. | d. |
|---|---|---|---|---|---|---|
| *Balance* due to Bank—13th May, 1905 | | | | 182 | 6 | 0 |
| *Meetings:* | | | | | | |
| Rent of Rooms | 73 | 10 | 0 | | | |
| Attendance at Laboratory Meetings | 3 | 14 | 6 | | | |
| Epidiuscope | 1 | 6 | 0 | | | |
| | | | | 78 | 10 | 6 |
| *'Transactions':* | | | | | | |
| Printing, Binding, etc., for Vol. LVI | 225 | 15 | 0 | | | |
| Illustrations " " | 65 | 16 | 4 | | | |
| | | | | 291 | 11 | 4 |
| *Secretariat and Treasury:* | | | | | | |
| General Printing and Stationery | 20 | 17 | 1 | | | |
| Council Notices | 2 | 0 | 0 | | | |
| Secretarial Assistance | 15 | 15 | 0 | | | |
| Collection of Subscriptions | 15 | 15 | 0 | | | |
| Mr. Clarke's Fee | 5 | 5 | 0 | | | |
| | | | | 59 | 12 | 1 |
| Contribution to Amalgamation Fund | | | | 5 | 0 | 0 |
| Bank Charges | 4 | 3 | 11 | | | |
| Sale of Consols per Power of Attorney | 0 | 11 | 6 | | | |
| Transfer of Consols | 0 | 10 | 8 | | | |
| | | | | 5 | 6 | 1 |
| Petty Cash Expenditure | | | | 7 | 12 | 2 |
| Balances | | | | 16 | 0 | 6 |
| | | | | £645 | 18 | 8 |

Audited and approved, May 28th, 1906.

P. H. PYE-SMITH, M.D., F.R.S., *Treasurer.*
S. G. SHATTOCK, *Hon. Secretary.*

S. N. BRUCE,
T. W. P. LAWRENCE, } *Auditors.*

Amount invested in Consols.. .. .. £629 16s. 10d.

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# REPORT.

## SESSION 1905–1906.

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1. *On the blood-glands as pathogenic factors in the production of diabetes and obesity.*

By Arnold Lorand (Carlsbad).

CORRIGENDA.

P. 69: second line from bottom, *for* calcares, *read* calcaria.
P. 72: in description of Fig. 15, *for* masculinum, *read* masculinam; *for* calcares, *read* calcaria.
P. 84: in description of Fig. 22, *for* anatis maris cauda, *read* anatis feminæ cauda.
P. 95: eighteenth line from top, *for* fled, *read* led
P. 105: seventh line from bottom, *for* Salamo fario, *read* Salmo fario.

[illegible] differentiation may disappear: women may acquire some of the attributes of the male sex—*e. g.* moustache and male voice; and at times it is difficult to tell the sex by the outward appearance. If infantilism is attributable to the non-development of certain blood-glands, senility is also related to changes in the same. According to Sir Victor Horsley (7) and Vermehren (8) senility is due to degeneration of the thyroid. I consider, moreover, that primary degenerations of other blood-glands produce the symptoms of senility in a secondary manner (9).

# REPORT.

## SESSION 1905–1906.

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1. *On the blood-glands as pathogenic factors in the production of diabetes and obesity.*

By ARNOLD LORAND (Carlsbad).

### I.

### Remarks on the influence of the blood-glands upon the processes of metabolism.

THAT our external appearance, and the attributes of sex, are the outcome of the internal secretion of the reproductive glands, has been urged by several authors: Halban (1), Ribbert (2), Foges (3), Sellheim (4), A. Loewy (5), and recently in a very convincing way by Shattock and Seligmann (6).

Infants and young children of both sexes have very much the same appearance, and in many cases it is only possible to detect a difference in their external appearance after the advent of puberty. After the climacteric age, however, this differentiation may disappear: women may acquire some of the attributes of the male sex—*e. g.* moustache and male voice; and at times it is difficult to tell the sex by the outward appearance. If infantilism is attributable to the non-development of certain blood-glands, senility is also related to changes in the same. According to Sir Victor Horsley (7) and Vermehren (8) senility is due to degeneration of the thyroid. I consider, moreover, that primary degenerations of other blood-glands produce the symptoms of senility in a secondary manner (9).

Aged persons have been compared to infants; the comparison is confirmed by the fact that in the aged, colloid substance is scarce in the degenerated thyroid, or sometimes entirely absent, whilst in the thyroid of infants it has not yet appeared or is present only in very small quantity.

Milk food is the best in both cases, as also in all myxœdematous conditions brought about by disease of the thyroid, or by surgical operation, or experiment. The sexual glands and the thyroid also influence the growth of the skeleton; for if the sexual glands are removed, the extremities become abnormally long—*e. g.* in eunuchs. Poncet (10) also produced this condition experimentally in the hind legs of rabbits.

Similar phenomena also occur in infantilism (type Lorrain) in which, according to Hertoghe (11), the thyroid plays a considerable part in addition to the atrophy of the testicles. Alterations in the growth of the skeleton have also been shown to occur after castration by Sellheim; whilst Lounois and Roy (12) have found an abnormal persistence of the epiphysial cartilages in persons with atrophied testicles, and Poncet has found the same condition in castrated guinea-pigs and cocks. The same phenomenon has been noted by Hertoghe, Springer, and Serbanesco (13), Gasne and Lande (14), Légoy and Regnault (15), and lastly by Jeandelize (16) in athyroidean conditions. Hertoghe (11) in such cases, by giving to children thyroid extract, produced marvellous growth—as shown by illustrations in his interesting monograph. Gauthier (17) has shown satisfactorily the effects of the thyroid upon the production of callus after fractures. I should like to point out here, to illustrate certain facts that I shall mention later, that diabetes has, as far as I know, not yet been observed in cases which show the above conditions. On the other hand, tuberculosis is more often met with in children who are backward in physical and mental growth on account of thyroid deficiency inherited from parents with cachectic diseases —*e. g.* syphilis, tuberculosis, malaria, etc. This fact points to the antagonism existing between diabetes and tuberculosis, a point upon which I have already insisted (18); diabetic persons may become tuberculous, but tuberculous persons very seldom become diabetic or gouty. Thus, if thyroid deficiency predisposes them to tuberculosis, they seem to possess a certain immunity to diabetes and gout. A fact that makes this clearer

is that Perrando (19) has found degeneration of the thyroid in the fœtus coming from parents with cachectic diseases, especially syphilis. Garnier (20) has also found that the thyroid in hereditary syphilis is degenerated and contains no colloid substance at all.

It seems that children coming from such parents have a diminished immunity against infectious diseases, for tuberculosis, as was mentioned above, readily develops in them. This is connected with the fact that in myxœdema (athyroidea) tuberculosis appears frequently, as shown by Greenfield (21) and Byrom Bramwell (22); according to Pel (23) tuberculosis is very frequent in the families of myxœdematous persons.

Experiments also illustrate these facts. Thus it has been found by several authors that animals whose thyroid has been extirpated easily fall victims to infective processes. The great part taken by the thyroid in infections is shown by the researches of Bayon of Würzburg (24) and de Querrain, which establish the fact that in all grave infectious diseases the thyroid is in a condition termed by them "thyroiditis simplex" without any suppuration. Roger and Garnier (25) had found previously to the former authors a hypersecretion of colloid in the thyroid in infectious diseases, which after some time may be followed by exhaustion of the gland. Logically there must be symptoms in infectious diseases indicating clinically the pathological changes in the thyroid. In my previous works (26) I have pointed out that in most cases of infectious disease symptoms occur which indicate an increased function of the thyroid—that is, symptoms of hyperthyroidea which resemble to a great extent those of Graves's disease, such, for instance, as hyperthermia, tachycardia, sometimes slight exophthalmos, perspiration, occasionally diarrhœa, and diuresis, sometimes amounting to polyuria. Hyperthermia may often be very pronounced in Graves's disease. A short time ago I saw in the wards of Dr. Hector Mackenzie a young girl with Graves's disease lying on the open balcony of St. Thomas's Hospital facing the Thames in mid-winter (although not on a very cold day), with her cheeks crimson red and very hot, a condition quite the contrary to that in myxœdema. These symptoms of infectious diseases indicate, I believe, a natural remedy of powerful character; the hyperthermia followed by transpiration, by diarrhœa, and by polyuria is an endeavour to

eliminate noxious agents. Symptoms such as those shown here are the necessary consequence of disease, and very often they are the expression of self-defence. If we were only to follow Nature, we should not always check her healing tendencies by means of antipyretics.

To complete my remarks on the problem of heredity and immunity, I may mention that in my previous works (27) I have tried to show that we inherit the pathological characters of the blood-glands from our forefathers. Put into practical words, this means that persons having inherited healthy blood-glands, including a good working thyroid, will have more immunity against infective diseases than others. These assertions seem to be confirmed by the recent experiments of Professor Lanz (28), the late assistant of Professor Kocher, of Berne. On removing the thyroid of animals he has found that their descendants remain backward in growth. Similar results appear in children of parents with diseases of the thyroid—*e.g.* goitre. The children of cretinoid parents, as a rule, develop neither physically nor mentally, but by giving them thyroid extract we see wonderful results in growth and mental ability. From symptoms seen in animals the thyroid of which has been extirpated, and, on the other hand, in persons who have been treated with thyroid extract, we must come to the conclusion that the thyroid influences the functions which, according to our present physiological ideas, we connect with the cortex of the cerebrum—*i. e.* intelligence, will power, imagination, memory, sleep, etc. In fact, in myxœdema or in animals deprived of the thyroid we see apathy, torpor, loss of memory, somnolence, etc. Moreover, the serum of animals the thyroid of which has been extirpated produces similar symptoms, and according to my experience this serum has distinctly hypnotic properties.

By giving thyroid extract we can remedy the above-mentioned mental defects.

Experimentally it has been proved by Walter Edmunds (29) that if the thyroid is taken away, symptoms of great disorder in the central nervous system may appear, of which I may mention: congestion of the blood-vessels in the cortex, degeneration of the nerve-cells with destruction of their processes, chromotolysis, and disappearance of the Nissl bodies, etc.

Clinically it is a well-known fact that alterations of the thyroid

are invariably followed by nervous disorders, as in Graves's disease and myxœdema. The frequency of nervous disorders in diabetes is also connected with this fact, as will appear later on. As the characters of the thyroid may be inherited, it is also clear why the children of such persons should show a predisposition to nervous diseases. If diabetes is a disease which in the majority of cases is developed on an inherited basis, and if children of diabetic persons are often of nervous disposition, these facts are dependent upon the important part taken by the thyroid (hyperactivity) in diabetes. These children are of quite a different constitution to those above mentioned which inherit thyroid deficiency. This appears in the bright intelligence, as a rule, of the children of diabetics in comparison with those of syphilitic or tuberculous parents, and in other details—*e. g.* the teeth of children of the latter are often irregular, and readily become carious.

If nervous diseases are not infrequently inherited, it may be explained by their arising on the basis of a thyroid which is the seat of inherited change. Besides the thyroid, the hypophysis (as seen in acromegaly) and the sexual glands exercise an influence on the nervous system. Any changes in the sexual glands may be followed by nervous symptoms, as appears from the psychical troubles which not seldom accompany gonorrhœa, prostatitis, and varicocele. Castration of the adult male may be followed by melancholia.

Similar facts are forthcoming in the case of the ovaries; and it is well recognised that puberty, menstruation, pregnancy, lactation, and the climacteric are prone to be followed by nervous diseases which may assume the character of mental disorders. As is well known, the sexual glands stand in close relationship with the other blood-glands, especially with the thyroid, which, as a rule, is also involved in the conditions above mentioned, and shows enlargement resulting from over-function, which might be followed by its exhaustion, as occurs after repeated pregnancy, prolonged lactation, etc. According to Ord (30), Morvan (31), Combe (32), myxœdema often thus results. The greater frequency of Graves's disease and myxœdema in women is thus, possibly, to be accounted for. Besides the sexual glands and thyroid, other blood-glands may be altered during pregnancy—*e. g.* the hypophysis (Launois), and adrenals (Guieysse [33] and

Minervini). Such facts may also explain why the marks of senility often appear earlier in women than in men, whose sexual glands, thyroid, and other blood-glands are not subjected to such a strain. Nervous disorders, again, like neurasthenia and hysteria, are, for a like reason, more common in women. In the case of criminal actions in women it should be ascertained whether these physiological conditions have any relationship with them.

Not only is the nervous system but the processes of oxidation are powerfully influenced by the blood-glands. After thyroidectomy, or in myxœdema, oxidation is diminished (Magnus-Levy [35]). In Graves's disease, on the contrary, and after thyroid medication, as found by the same author and by Mattes, and previously by Vermehren, oxidation is increased. Oxidation is likewise diminished after castration (Loewy and Richter [36]); the administration of testicular extract to the castrated dog, however, increases oxidation, and still more does ovarian extract in the castrated male dog, whilst ovarian extract of course effects an increase of oxidation in the spayed bitch.

According to Poehl (37), Prince Tarchanoff, and others, spermin also increases oxidation. Narbuth (38) states that the same holds true in regard to the hypophysis.

The pancreas exercises a powerful influence upon the metabolism of carbohydrates.

Its total extirpation, as demonstrated by Minkowski and Mering (39), is followed by severe diabetes; and its partial extirpation or degeneration by light diabetes or alimentary glycosuria. The pancreatic origin of diabetes has been disputed, because in some cases no macroscopic changes appear in the pancreas. It has been shown, however, by Schäffer, Laguesse, Opie (40), Weichselbaum (41), and others, including myself, that in most of such cases there are microscopic changes in the islands of Langerhans which, like the parathyroid, adrenals, or interstitial cells of the testicle, represent blood-glands. The ordinary secreting tissue of the pancreas may be destroyed in cirrhosis without involvement of the islands, as in an example in the Vienna Pathological Institute. In this case no diabetes was present; but in another from the wards of Professor Minkowski at the Augusta Hospital in Cologne, in which besides cirrhosis there was involvement of the islands, light diabetes was found.

When no change in the islands is discoverable, it may be that during life the gland was nevertheless not properly functionating. Every gland secretes under a nervous influence. As shown by Pawlow, there exists in the dog a psychic gastric and also a psychic pancreatic juice. Now, the pancreas is mainly controlled by the sympathetic (splanchnic), which is also the main nerve-supply of other blood-glands, and it may be difficult after death to discover whether any abnormal innervation has obtained during life and led to deficient secretion. Hence the contrary findings by Hansemann (43), Herscheimer (44), Karakascheff (45), and others do not invalidate the great importance attaching to the islands of Langerhans. According to Professor Ebner, of Vienna, these islands aid in the metabolism of carbohydrates, and Sobolew found that in animals the islands diminish in size after the administration of rich carbohydrate food. We may thus explain, as I have insisted elsewhere (46), why diabetes will develop more readily in those who have been living a long time on much carbohydrate food.

Diamare and Kuliabko (47) have found by experiments at the zoological station in Naples that extracts of the Langerhans islets in certain fishes aid in the inversion of grape-sugar. Hence we must conclude that the Langerhans islets probably provide the internal secretion of the pancreas, which is indispensable for the metabolism of carbohydrate food.

## II.

### On the relation of the blood-glands to diabetes.

As has been shown by the researches of Pineles (48) and of myself (49), the various blood-glands stand in close relation to one another. Changes in one of them are, as a rule, followed by changes in others. Thus in acromegaly, in addition to the very frequent alterations in the hypophysis, there exist also changes in the sexual glands (impotence and amenorrhœa caused by pathological changes of the sexual glands), of the thymus (abnormal persistence), adrenals (frequent alterations found), pancreas (diabetes frequent).

The thyroid, according to my researches, is altered almost constantly, more frequently, I should think, than the hypophysis. These alterations are, in my opinion, primary and lead in a

secondary manner to those of the hypophysis, in the same way as in the experiments of Gley (50), Hofmeister (51), Rogowitch (52), and Stieda (53) on animals.

As I have shown previously (54), diabetes only occurs in those cases of acromegaly in which there also exist symptoms of hyperthyroidea (Graves's disease), whereas it is always wanting in cases of acromegaly accompanied with myxœdema.

In those cases of acromegaly with diabetes where the thyroid and the pancreas have been examined these organs have been found in an altered condition; the pancreas has been found degenerated, and the thyroid hypertrophied, with much colloid, as in the cases of Pineles (55), Hansemann (56), Ferraud (57), Harlow Brooks (58), Dallemagne, etc.

In diabetes, beside the alterations in the pancreas, there exist symptoms which indicate changes in the sexual glands (impotence and amenorrhœa). If certain blood-glands are found degenerated in diabetes, on the other hand, there are other blood-glands the extracts of which may produce glycosuria or diabetes. Thus it has been found by Blum (60), Zuelzer (61), Metzger (62), Herter, and Wakeman that the injection of adrenal extract may produce considerable glycosuria in animals. The extract of another blood-gland, moreover, viz. the thyroid, may produce, even in a higher degree than adrenal extract, glycosuria and even its higher degree—true diabetes. According to Naunyn (64), Van Noorden (65), Strauss (66), and Goldschmidt, diabetes only follows in such cases when there is an inherited predisposition. It is an interesting fact that by giving thyroid extract all the symptoms of true diabetes can be produced.

I have under observation a case of acromegaly in which the urine was found free of sugar in September, 1895, and in which much sugar was found towards the end of October. This patient was given thyroid tablets in the treatment of his acromegaly in October; this treatment was commenced more than ten years ago, and for eight years this patient has been excreting acetic acid and acetone in quantity. He had no glycosuria before the commencement of treatment with thyroid. The long duration of his severe diabetes, joined with his acromegaly, make the case very interesting. Glycosuria is frequent in Graves's disease, but generally in cases of not long duration. Alimentary glycosuria seems to be more frequent. According to Van Noorden there

exists an unusual tendency to alimentary glycosuria in Graves's disease. In this disease also diabetes is not very rare. In cases of Graves's disease which are of long duration and are passing into or are combined with myxœdema, glycosuria is rare. A very instructive case of this has been published by Schrotter (68), where there was no glycosuria after administration of 200 grains of grape-sugar. In such conditions, as also in myxœdema, diabetes is extremely rare. J. Hirschl (69), of Vienna, has found glycosuria in six cases of Graves's disease, but in none of four cases of myxœdema could he produce alimentary glycosuria. Knopfelmacher (70), also, could not produce alimentary glycosuria in myxœdema even by means of very large doses of grape-sugar.

In the cases recorded by Ewald (71) and Beclère (72) (myxœdema with diabetes) diabetes was produced by treatment with large doses of thyroid extract. It is interesting that diabetes or glycosuria is common in all conditions of hyperthyroidea, and equally rare in the opposite condition of athyroidea. Thus glycosuria or diabetes is frequent in infectious diseases (the result of action on the thyroid, as mentioned in the foregoing chapter), after toxic agencies (acting on the thyroid according to Garnier), after mental emotions (well-known effect on the thyroid, demonstrated also by the frequency of Graves's disease after such). The increase of glycosuria during menstruation, its appearance during lactation (lactosuria), and occasionally during pregnancy, is related to the increased thyroid function accompanying these conditions. Manchot (73) has observed glycosuria during syphilitic eruptions in women; this may be explained by the statement of Engel Reimers (74), who noticed swelling of the thyroid in women with this condition. Glycosuria has been observed during biliary colic by Gans (75), Finkler (76), Exner (77), and may be explained by the fact, demonstrated by Hurthle (78), that stagnation of the bile causes an increased secretion of thyroid colloid. It is an interesting fact, found by Moussu (79), that after thyroidectomy in a goat the milk gets poor in sugar but rich in fat. If glycosuria or diabetes is frequent in hyperthyroidea, on the other hand, they are rare in all conditions of athyroidea or hypothyroidea. This is true in myxœdema, as above mentioned, and in cretinism, for Scholz (80) was unable to produce glycosuria or the symptoms of hyperthyroidea in one hundred cretinous children.

Degenerative changes are met with in the thyroid in chronic tuberculosis (Roger and Garnier [80 *a*]) and myself (81), and also in cancer (myself). This fact may explain why diabetes is so rare in either of these diseases, which may follow diabetes, but seldom precede it. The diminished excretion of sugar at the close of diabetes, before death, or in opium-poisoning depends upon the diminution of thyroid secretion. Over-activity of any gland may be followed by its exhaustion. Thus hyperthyroidea (Graves's disease) may be followed by athyroidea (myxœdema). This may also happen after the over-action of the thyroid in diabetes.

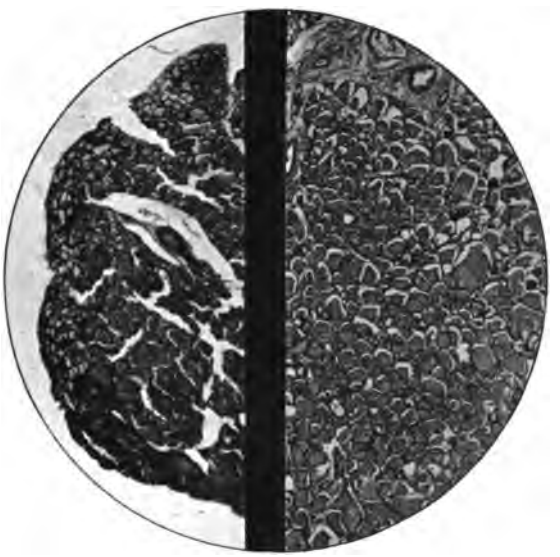
Hence, if the symptoms of diabetes in general resemble those of Graves's disease, in the advanced stages they may approximate to those of myxœdema—dryness of skin, coldness of extremities, loss of hair and teeth, apathy, loss of memory for recent events, red patches on the cheek, torpor, headache, etc.

When severe diabetes is so far advanced that such a condition appears (though it need not do so in all cases), the sugar in the urine might also diminish, but not the acetic acid and acetone, which might even increase. Under such circumstances tuberculosis may easily arise, and it is interesting that in such cases there is then a further diminution of sugar; there are cases of diabetes where the sugar may disappear after the onset of tuberculosis. In the early stages of myxœdema there is often obesity, but in the advanced there is cachexia with emaciation, as in animals after thyroidectomy. If one blood-gland is changed, others will also show alterations. During life I have often observed in cases of light diabetes a slight or greater enlargement of the thyroid, and in a few cases the appearance of a goitre. According to George Murray the thyroid is bigger in women than in men; my own observations confirm this. The larger size may be related to the functions of the sexual glands. It is not easy to examine the thyroid during life; what is apparently a small thyroid may turn out to be a large one. In Graves's disease the thyroid is not always obviously enlarged. On the other hand, cretins may have a very large thyroid, but the latter consists not infrequently of connective tissue without colloid substance; this shows that the large size of the thyroid is no proof of its over-action.

On examining the thyroid of three dogs in the laboratory

of Professor Minkowsky, at Cologne, after the extirpation of the pancreas, I found in each a considerable enlargement of the vesicles and much colloid. In one case, that of a male puppy of two months, these alterations were very considerable, as told by comparing the thyroid with that of another male puppy of the same litter and same age. I may especially draw attention to the fact that the latter animal was chloroformed, and that, as a rule, an enlargement of the thyroid is more or less

FIG. 1.



Sections of two thyroid glands. That on the left is from a healthy male puppy killed with chloroform; that on the right is from a puppy of the same litter, the pancreas of which had been excised; its vesicles are markedly distended with colloid.

distinctly observable after chloroform narcosis. The increase of colloid in the latter case, however, is not by any means so great as in the former, in which the thyroid was removed after death.

Another dog in the laboratory of Professor v. Noorden, of Frankfort, which was kept fasting six days after extirpation of the pancreas, also showed similar alteration in the thyroid. The thyroid of these dogs shows a similar picture to that of the fowls of Chalmers Watson (83) after meat-feeding. If the results are not similar to those in the rat, it must be borne in mind that the thyroids of the dogs were taken away a few days after the extirpation of the pancreas. But as over-function will be followed

by exhaustion, it is not unlikely that if these dogs were to live very long the thyroid would show similar changes to that of the rats in Chalmers Watson's experiments. We must also remember that rats are carnivorous, and that the thyroid, as is the rule in carnivora, would produce a larger amount of colloid. In the early stages of Graves's disease I have seen (in the laboratory of Professor Langerhans in Berne) similar changes in the thyroid to those of the dogs in my experiments and the fowls in Chalmers Watson's. In the later stages of Graves's disease the thyroid would naturally look different, and no longer produce normal colloid. The same thing may take place also in diabetes. If Graves's disease is a condition of hyperthyroidea, there would be an entrance of colloid in large quantity into the system. The colloid is the real secretion; according to Oswald (84) the principal element of the thyroid, the iodine, depends entirely upon the amount of colloid in the gland. The absence of colloid in myxœdema I view as the result of an exhaustion following hypersecretion. Hence myxœdema may follow infective diseases, mental emotions, grief, and oft-repeated pregnancy, since in all of these conditions there is hypersecretion of colloid.

In Graves's disease the increased secretion constitutes a toxic agent, and produces results like those arising from the use of large doses of thyroid tablets. There results, as shown by Magnus-Levy (85), a decomposition of albuminous substances: the carbohydrate radicle, the existence of which in the albuminous molecule has been deinonstrated by Pavy (86), is set free. If the pancreas is active, diabetes might not follow, or only slight glycosuria, according to the amount of the toxic substance absorbed; but if the pancreas is degenerated or has been removed, the sugar that has been set free will appear in the urine.

These facts show that certain relations exist between the pancreas and thyroid, which seem to be of an antagonistic nature, since extirpation of the pancreas is followed by alterations in the thyroid like hypertrophy, with abundant production of colloid. On the other hand, in one case (dog) of thyroidectomy I have seen an extraordinary number of Langerhans islands in the pancreas, some of them very small, as though a new formation were in progress. I may add to this the experiment of Quinquaud (87), and the later ones of Kishe (88), who found the pancreas hyperæmic after thyroidectomy.

In the wards of Professor v. Noorden I have seen a case of Graves's disease in which after a few years diabetes appeared. After death calculi were found in the pancreatic duct and the gland itself was degenerated; here hypertrophy of the thyroid and degeneration of the pancreas coexisted. In the hospital at Hanover I lately saw a woman who presented typical symptoms of Graves's disease, and who, as Dr. Paulsen told me, became subject to severe colics, which he took to be pancreatic; the urine contained 3 per cent. sugar.

I regard it as of importance that in the three diabetic dogs whose thyroids were removed, without the parathyroids, the sugar disappeared from the urine on the second day following the thyroidectomy. One of these dogs lived for three days free of sugar in the urine; even after about 200 grms. of milk had been administered the urine gave only a feeble reduction. That none of the diabetic dogs lived longer than four days after the thyroidectomy must be attributed to the loss of two such important organs. I am not sure, however, whether this disappearance of the sugar was not merely terminal, seeing that in the cadaver of diabetics sugar is often found even when it has diminished before death. In dogs, also, after extirpation of the pancreas, in exceptional cases sugar may not be found. These exceptions, however, can hardly affect the regularity of the sequence in my experiments.

Moreover, in those cases when before death sugar entirely disappears the thyroid may also cease secreting. I conclude that there are two important pathogenic factors in diabetes—(1) degeneration of the pancreas: (2) hyperactivity of the thyroid. If the pancreas alone is degenerated and there is no hyperactivity of the thyroid, the diabetes will be a light one. This is the case in the diabetes of old persons, which is in most cases due to arteriosclerosis of the pancreas. As Sir Victor Horsley first pointed out, the thyroid in old age shows degenerative alterations, although this is not the case in every person beyond a certain age.

If in addition to the pancreatic degeneration the thyroid is over-active, the diabetes will be severe. This is the case in young persons whose thyroid is in good working order.

When there exists only hyperactivity of the thyroid, as in Graves's disease, or often mental emotions, there may be only

glycosuria, spontaneous or alimentary, but if this is added to a degeneration of the pancreas on an inherited basis or on one acquired by syphilis, arteriosclerosis, etc., diabetes will follow.

It should be mentioned that in cases of Graves's disease with diabetes, when these glands have been examined, the pancreas has been found degenerated and the thyroid hypertrophic, as in the case of Morris Manges (89).

Similar facts have been found to hold in acromegaly. In regard to the relationship of glycosuria to diabetes it must be borne in mind that there exists no sharp demarcation. Diabetes often begins as simple alimentary glycosuria.

Lastly, I may mention that in a series of diabetic cases (26) I have employed the antithyroidin serum of Moebius, as also the rodagen of Burkhard Blumenthal made of the milk of goats after thyroidectomy. The nervous symptoms have been ameliorated, especially the insomnia, and the glycosuria has diminished or has disappeared. As the Carlsbad water, however, has been employed simultaneously, the cause of the result is not clear. Nevertheless I think the antithyroidin serum is capable of diminishing glycosuria, but I should not advocate its use in advanced cases of severe diabetes accompanied with cachexia, this condition being near to a myxœdematous one.

Chalmers Watson has recently added experimental proofs to my clinical observations (90) upon the increased activity of the thyroid following a meat diet.

Diabetes, as I have pointed out, will more readily occur in persons who take much meat, especially if they take large quantities of carbohydrates. Hence after extirpation of the pancreas in birds, diabetes will appear only in those which are carnivorous, as in birds of prey, and not in ducks, pigeons, or geese.

Animals may acquire diabetes spontaneously, especially those taking much albuminous food, like the fox-terrier of Naunyn (91), which lived on rice and meat, and the monkey of Beranger Férand (92). Monkeys, in Europe, usually die of diabetes. This I attribute in part to their vegetarian habits. Among the monkeys of Signor Volpi, at the Royal Italian Circus of London, those which were kept on meat or other albuminous food did not succumb to tuberculosis. Hence if much proteid predisposes to diabetes or gout it is a powerful preventive against tuberculosis. I know of a case, also, of spontaneous diabetes in a large St.

Bernard dog, which, since a puppy, had been brought up upon meat with a daily pot of cream and much sugar; the symptoms were polyuria, thirst, and loss of weight. According to Bosc (93) diabetes is rare amongst the poorer Indians, who live on rice only, but frequent among the rich, who live on rice and meat.

## III.

### On the relation of the blood-glands to obesity.

It has been long known that domesticated animals are fattened by removal of the sexual glands. The same is true of the human subject, both male and female. The explanation of this, according to Loewy and Richter (36), is that diminished oxidation ensues. The same result follows removal or disease of the thyroid. That oxidation is diminished in myxœdema has been shown by Magnus Levy (35), who has shown also that it is increased in Graves's disease. Removal of the thyroid leads to obesity. In animals there follows a mucinous and fatty infiltration of the subcutaneous connective tissue. Hertoghe has lately observed that a young bull put on 20 kilos in a few months after thyroidectomy; the same author has made a like observation on the horse.

So, too, clinically in the early stages of myxœdema there is often a considerable degree of obesity associated with the formation of fatty tumours. In fat pigs Lanz (93) has found atrophy of the thyroid. Abrikosow (94) has recently described a case of myxœdema in a woman, aged 52 years, in whom the obesity was extreme, and in whom after death fat was found in the submucous tissue of the intestine and mucous membrane of the tongue. Bourneville and Lemaire (95) have described cases of dwarfing associated with athyroidea and marked obesity. Complete athyroidea is somewhat rare, but an advanced destruction and degeneration of the thyroid is, I think, common. The work of Blum (96), Breisacher (97), and Kishi (98) shows that the thyroid acts as a deintoxicatory organ against the poisons arising from the decomposition of proteid food. The degeneration may be slowly progressive. The progress of myxœdema may be very insidious and slow, like that of other diseases arising from lesions of the blood-glands.

According to the number of vesicles of the thyroid affected there will be different degrees or forms of myxœdema. Reverdin (99), Combe, Chantemesse, and Marie have described a "myxœdema fruste," and Hertoghe a "hypothyroidie benigne chronique" to the symptoms of which obesity belongs. In his classical work on myxœdema George Murray gives the picture of a myxœdematous woman affected with obesity. Brissaud distinguishes a partial myxœdema; Marfan and Guinon (100) have published the case of a child with partial myxœdema and extreme obesity. An instructive case has been recorded by Schrötter (68), of Vienna, in a woman suffering from Graves's disease, in whom the upper part of the body was emaciated and pigmented, whilst the lower part was highly obese; simultaneously there were present other marks of myxœdema, such as desquamation of the skin on the eyebrows; the thyroid felt as if partially fibrous. This case was, I believe, one of transition to myxœdema. Such have been described by Kowalewski (101), Baldwin (102), Sollier (103), Christian Ulrich (107), and others. The obesity of senescence may be associated with senile fibrosis of the thyroid and fatty change in its epithelium, as shown by Sir Victor Horsley; this has been found also by Erdheim (105) in the parathyroids and the hypophysis (106) of aged persons, a fact also observed by Launois. The retrogression of the sexual glands has also to be taken into account.

As before observed, intimate relations subsist between the sexual glands and the thyroid; over-function of the ovaries may be followed by their exhaustion, and as an associated result the thyroid will undergo premature degeneration. This may explain why women, as a rule, become senile and grow more often fat than men. Thus obesity may follow frequent pregnancies and prolonged lactation; these are also frequent causes of myxœdema, according to Ord (30), Morvan (31), Coombe (32). Regaud (107) has found atrophy of the testicle in the guinea-pig when kept in complete sexual abstinence. There is much clinical evidence for the supposition that total suppression of the function of the sexual glands may affect the nervous system, as shown by the production of neurasthenia and hysteria. These diseases seem also to be more frequent amongst the unmarried between thirty and fifty, especially women.

Obesity occurs after various conditions which produce degenera-

tive changes in the sexual glands, as after the menopause; accompanying the changes in the ovaries, there would be modifications of the thyroid. Obesity may also arise after the convalescence from infective diseases as a result of the thyroid degeneration due to the disease itself. According to the examinations of Roger and Garnier (25), confirmed by Crispino (109) and Torri (110), a hypersecretion of colloid may be met with in such diseases, but this may be followed by exhaustion of the gland. Infective diseases may also lead to modifications in the sexual glands. Cornil has seen menstruation with abundant metrorrhagia in the early stage of typhoid, and at the autopsy a few weeks later a very voluminous corpus luteum.

Involvement of the sexual glands in infective conditions is also illustrated by the experiments of Metschnikoff (112); on injecting tetanus bacilli in large quantity he found them in the ovaries of female animals and in the testicles of the males. According to Loisel (113) the ovaries play the part of clearing the organism of noxious agents, endo- and exo-toxins. Obesity following convalescence from infective diseases may thus be due to modifications in the sexual glands as well as to thyroid degeneration.

There is a third gland which seems to stand in some relation with obesity, viz. the hypophysis. Thus in cases of acromegaly obesity may arise. Even in cases of tumour of the hyphophysis, without acromegaly, obesity may be met with. In 1841 such were described by Mohr (114). Fröhlich (115) has collected a number of such cases published by Hippel (116), Gläser, Boyce and Beadles (117), Pechkranz, Stewart, Walton, Cheney, and to these he added another of his own. In addition, such cases have been recorded by Eisenlohr (118), Roth, Ingermann, Cestan and Halberstadt, Babinski (119), Selke, Strümpell (120), Zak, Burr, MacCarthy and Erdheim (106). Berger (121) has published an example of tumour of the hypophysis associated with obesity, and Madelung (122) a case of great development of subcutaneous fat in a girl, aged 9 years, following gun-shot injury of the hypophysis. On the ground of the foregoing clinical observations I am inclined to distinguish two categories of obesity—(1) the exogenous, (2) the endogenous.

The first is that arising from rich living, especially carbohydrate food, combined with little exercise. The second is seen

in those who eat little yet continue to grow fatter, and is due to degeneration of the blood-glands which regulate the process of oxidation. Persons of the first category are red in the face and plethoric. Those of the second are usually pale and feel cold, with no tendency to perspire; their fat is firm, or like bacon. Pronounced cases of this kind might, I think, be called bacon obesity; these patients are especially benefited by thyroid treatment. Thyroid treatment in persons of the first category might lead to glycosuria or even to diabetes, though in such this would not be of great intensity. Diabetes, on the other hand, is rare in persons of the second class. The endogenous form of obesity may be reckoned as a disease due to morbid conditions of certain of the blood-glands.

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## 2. *True hermaphroditism in the human subject.*

By T. W. P. Lawrence.

*De hermaphroditismo vero apud homines.*

### Summarium.

Genitalia male evoluta; in perinæo aperitur sinus urogenitalis quo et urethra et vagina communicant.

Uterus unâ cum tubâ Fallopii dextrâ, normalis; tuba sinistra, exigua.

In uteri cervicis pariete (in parte sinistrâ) inclusus adest ductus qui in ligamento lato sinistro jacet, et apud extremitatem patulam tubæ Fallopii sinistræ terminatur. Ductus illius extremitas insigniter convoluta est. Has structuras vas deferens et epididymem esse opinamur.

In utrâque parte adest glandula generativa.

Illa dextrâ infra tubam Fallopii jacet, et ovarii figuram præsentat.

Corpus exiguum glandulam inter et tubam in situ parovarii ponitur.

Sectio probat microscopica glandulam ex stromate constare in quo adsunt cellularum epithelii collectiones inter se connectæ et e cellulis duorum generum constitutæ. Harum cellularum alteræ, parvæ, multiformes; alteræ grandiores sunt. In glandulæ cortice hæc duo genera cellularum sine ordine disponuntur; quibusdam in locis folliculi discerni possunt quorum quisque cellulam grandiorem, sive ovum, includit.

Hanc glandulam ovarium esse opinamur.

Glandula sinistra in duas partes dividitur. Portio altera structuram eandem ac illam jam descriptam præsentat; hanc, ergo, quoque ovarium esse putamus. Portio glandulæ altera, grandior, aliam structuram habet. In stromate jacent tubuli flexuosi membranâ limitanti circumtecti. Hanc portionem credimus testem, et glandulam totam ovotestem esse.

Cellulæ in mediis tubulis, parvæ, ac sine ordine disponuntur; illæ ad membranam limitantem multiformes aut subcylindricæ sunt, basibus ad membranam pressis. Tubuli quidam lumen ostendunt. Apud glandulæ marginem fixam tubuli minores sunt et rete male definitum construunt.

Omnium casuum hermaphroditismi veri adhuc descriptorum indagatio indicat (ut opinamur) quod quinque modo (exemplo nostro incluso) pro certo haberi debeant.

Sequitur horum cataloga.

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Medical literature contains the records of no less than thirty-three cases of malformation of the genital organs in the human subject, which are put forward by the authors as examples of true hermaphroditism. Yet, if inquiry were made, it would probably be found that most pathologists of the present day are sceptical as to the existence of true hermaphroditism in man. There can be little doubt that this attitude of mind, although it may be to some extent a result of the unsatisfactory character of many of these records, has its origin in the criterion which pathologists tacitly adopt in forming a judgment on any reported case of true hermaphroditism, namely that spermatogenesis and ovogenesis shall be shown to be present. The coexistence of spermatogenesis and ovogenesis has certainly never been demonstrated in any recorded case of hermaphroditism, and it is very doubtful if it was present in a single case of those above referred to. This fact may seem to justify in some degree a sceptical attitude; yet cases have been reported from time to time in which bisexual characters are marked with such distinctness that it might be supposed they would be accepted as at least presumptive evidence in favour of the occurrence of true hermaphroditism. Of such cases that recorded by Sir Hector Cameron[1] may be cited as being, perhaps, the most remarkable, though others hardly less so might be referred to. The patient, aged 27 years, had married a wife three years previously, but was without offspring. The external genitals were those of a male; the penis was fully developed and the prepuce normal. The scrotum was completely formed, but asymmetrical owing to the absence of the genital gland of the right side; the gland present in its left half resembled a testicle in form and consistence and in the presence of a structure having the form and relations of an epididymis; from the gland a cord could be traced upwards to the external abdominal ring. The pelvis was of the male type, and the development of hair on the face and body was such as occurs in the male. Erection of the penis was complete,

[1] 'Brit. Gynæc. Journ.,' 1903-4, vol. xix, p. 347.

and regular and normal intercourse took place, the act terminating in an emission. The presence or absence of spermatozoa in the fluid emitted is not recorded. The breasts were like those of a woman in size and shape, with large nipples and dark areolæ. This patient had suffered, since the age of thirteen, from recurring attacks of pain in the right iliac region; latterly these attacks had occurred regularly at monthly intervals and lasted twenty-four hours. Laparotomy having been performed, an imperfectly developed uterus was found, with normal uterine appendages on the right side, but none on the left. The ovary and tube were removed and the presence of Graafian follicles and ova in the former was demonstrated by Professor Muir.

The functional activity of the sexual glands, however, is not limited to spermatogenesis and ovogenesis, and a definition of true hermaphroditism cannot be regarded as sufficient which is based solely on a recognition of these two functions and disregards other important qualities which enter into the conception of sex. There is every reason to believe that the genital glands produce internal secretions, and by their means exercise functions of a distinctly sexual kind. The investigations of Shattock and Seligmann[1] point unmistakably in this direction; and although it is not at present possible to formulate the precise relations which secondary sexual characters and the sexual instinct bear to these internal secretions, it is in the highest degree probable that some definite relation exists between them.

From the foregoing remarks the main points to be comprised in a good definition of true hermaphroditism may be inferred. One point alone requires to be mentioned, namely, that the effects which are manifested in the body generally through the presence of the genital glands are not confined to those cases in which the entire organs are present, but that mere fractions appear to exert an influence hardly inferior to that of the whole gland.

True hermaphroditism may, therefore, be said to be characterised by the presence of the specific tissue of the ovary and of the testis in the same individual.

This definition, while embracing the points above referred to, imposes no limitations as regards the degree of functional activity exhibited by the sexual glands. Evidently their functional activity may vary, as in unisexual individuals, and it is at

[1] 'Path. Soc. Trans.,' vol. lvi, p. 57.

least probable, not only that ovogenesis and spermatogenesis may vary independently of the phenomena resulting from the internal secretions of the glands, but also that, in hermaphrodites, these phenomena may be, in a sense, the resultant of the activities of the two kinds of glands, and may vary according as the one or the other kind is the more potent.

Without attempting to examine how far recorded cases of true hermaphroditism correspond to this definition, it may be of interest to bring together within the limits of a single essay the descriptions of all cases of hermaphroditism which have an unquestionable claim to be regarded as "true," excluding those cases in which a histological examination is wanting or has been imperfectly carried out. The descriptions thus brought together represent the substratum of fact upon which a judgment must rest in deciding whether or not it can be truly asserted that the occurrence of true hermaphroditism has been demonstrated in man.

### *The case of Garré and Simon.*

The patient,[1] aged 20 years, had been reared as a male and showed distinctly male instincts; his general configuration was of the male type. From an early period the breasts had been unusually developed, the left more so than the right, and three years previously they had shown signs of temporary enlargement; a similar enlargement occurred subsequently from time to time. During the last three years an inconsiderable discharge of blood from the external genitals had occurred, usually at regular intervals of four weeks and accompanied with slight sacral pain; an emission of mucinous fluid had also taken place at irregular intervals, generally under the influence of sexual impulse towards the female, and accompanied with erection. The patient was of middle height and well proportioned, though with no pronounced muscular development. He was of fair complexion and without hair on the face, excepting slight indications of a moustache. The thyroid cartilage was not prominent. The thorax widened somewhat below, but its circumference at the base did not exceed that of the pelvis. The breasts had each

[1] 'Virchow's Archiv,' 1903, Bd. 172, S. 1; and 'Deutsche med. Wochenschrift,' 1903, No. 5.

a circumference of about equal extent; the right breast measured 3·75 cm. in height, the left 5·5 cm. Both breasts were of hemispherical form, and the left was somewhat pendulous; their consistence was soft, with firmer lobulated glandular portions. The nipples were retracted, the areolæ pink and not pigmented. The abdomen was devoid of hair to within a short distance of the pubic crest. The pelvis was broad; diameter spinarum 29 cm., diameter cristarum 34 cm., conjugata externa 17·5 cm., diameter intertrochanterica 35 cm. The subpubic angle was wide. At the symphysis pubis was a cylindrical body having the form of the penis, 4 cm. in length and 6·5 cm. in circumference; it exhibited a well-defined but imperforate glans of the size of a hazel-nut, which was covered on the dorsum by a fold of skin, incomplete inferiorly. A longitudinal cicatrix extended from the apex to the base of the penis on its under aspect. A fold of skin covered with hair was present on either side, below the penis; these folds, which measured 5 cm. in length, and together 3·5 cm. in breadth, united posteriorly in a broad commissure; in neither of them was a glandular organ present. On separating the folds a fusiform space was brought into view, its floor lined with skin from which hair was absent; two small folds of skin, measuring 1·5 cm. in length, were attached to the floor of this space and enclosed the apparently normal orifice of the urethra. A straight catheter passed into the urethra reached the cavity of the bladder at a distance of about 4 cm. At the right external abdominal ring a solid body could be felt of the size of a cherry, somewhat elongated in form, and having a smooth surface; it could be pushed back into the inguinal canal, but resumed its original situation on removal of the pressure. On examination *per rectum*, the folds of Douglas could be readily distinguished. On the left side an elongated, cylindrical body could be felt, having the thickness of a pencil, and about 4 cm. in length; superiorly it became somewhat thicker, while inferiorly it thinned off. This body was freely movable, and its lower cord-like end could be traced apparently to the urethra; above it a second body could be felt, which was of the size of a chestnut, freely movable, slightly irregular on the surface, and of the consistence of a genital gland. The two bodies appeared to be connected towards the upper end by a cord-like structure about 2 cm. in length. Nothing corresponding to a uterus could be felt in the middle

line, nor could anything be distinguished on the right side of the pelvic cavity, beyond the fold of Douglas. Some mucous fluid taken from the external genitals was examined microscopically and found to contain epithelial scales and cell-detritus. None of the emissions previously referred to occurred during the period in which the patient was under observation. In the fourth week of observation a scanty discharge of blood occurred, lasting one day and accompanied with sacral pain. An incision having been made in the right groin, the body before mentioned, enclosed in a sac of peritoneum containing a small quantity of clear fluid, was brought into view. It was of oval form, rather larger than a cherry, and had the consistence of a normal testicle; its surface was of a yellowish-brown colour, smooth and polished, and showed, at one spot only, a narrow cicatricial streak. To one end of it there was attached, without any definite line of demarcation, a whiter and firmer projecting portion or process, having the size of a pea. A broad, fibrous pedicle passed from this body into the abdominal cavity, and slight traction on this brought other objects into view, one of them being evidently a Fallopian tube; this measured 7 cm. in length and had an orifice at one end surrounded by short, thick fimbriæ. The other end of the tube became lost in a fold of peritoneum, which was also attached to the whole length of the tube, and was, doubtless, the broad ligament. Situated in the broad ligament was a somewhat flat structure measuring about one third the length of the Fallopian tube and occupying a position immediately below the outer part of the tube; it had the thickness of a pencil and rounded ends, and it projected ½ cm. beyond the free edge of the broad ligament; it appeared to consist of a complex interlacement of yellowish-grey strands and was regarded as the parovarium. From the surface of the broad ligament a broad pedicle passed to the before-mentioned oval body (genital gland), forming a deep pocket between the latter and the Fallopian tube, and from the genital gland a fibrous band passed into the abdominal cavity, and contained within it, besides vessels, a thin, firm strand which was apparently the vas deferens. Close to the vas deferens and at a distance of about 1 cm. from the genital gland, lay an irregular yellowish-white body of about the size of half a pea. A portion of this body and of the genital gland and its projecting process were excised for microscopic

examination, and the Fallopian tube and parovarium were removed. To the naked eye the section of the main portion of the genital gland was yellowish in colour and finely granular; its small projecting portion was firmer, greyish-white, and of streaked appearance. *Microscopic structure of the projecting portion of the genital gland:* An external fibrous capsule was present, composed of several layers of spindle-cells, mostly lying parallel with the surface. In some places remnants of a single layer of cubical epithelium were present on the surface. Beneath the capsule lay a richly nucleated connective tissue, the fibres of which were mostly arranged circularly around small globular structures. In the latter there could be distinguished externally a single layer of low epithelial cells with deeply staining nuclei, and within this layer a large globular cell with clear, non-granular protoplasm, granular nucleus, and deeply staining nucleolus. These bodies, which were evidently primitive follicles, were in some parts closely placed and in others separated by abundant stroma. More highly-developed follicles than these were not met with. *Microscopic structure of the main part of the genital gland:* Externally there was a capsular layer of firm connective tissue which became somewhat looser in its deeper part. Within this capsule the organ mainly exhibited sections of tubules lying in a characteristic stroma, which varied much in amount in different places. The stroma was composed of a loose and very delicate connective tissue containing small, scattered nuclei and presenting numerous capillaries and vessels of somewhat larger size. In the connective tissue there were small collections and strands of large epithelioid cells, with slightly granular protoplasm and round well-stained nuclei; in these cells needle-shaped crystals could be seen, having in places a rhomboidal section. The tubules varied in form, some being circular, others elongated, a few S-shaped, the majority having a reniform outline. The diameter of the tubules varied little, but the thickness and structure of their walls showed great differences. In some the wall consisted of layers of concentrically arranged connective-tissue cells bounded by a homogeneous membrane; between the cells a delicate elastic network could be demonstrated by Weigert's method. In most of the tubules the wall consisted of a thick hyaline layer, with little or no trace of connective-tissue cells or elastic substance remaining, the thicken-

ing of the wall resulting in a diminution of the lumen, in some cases almost to complete obliteration. The epithelium contained within the tubules was disposed in numerous layers, and in many instances entirely filled the lumen; the cells lay in close apposition, the contours of individual cells were badly defined, and their finely granular protoplasm appeared as a reticulum containing round or elliptical vacuoles. The nuclei were elliptical and stained well; here and there rather larger, round, vesicular nuclei were met with. From some of the tubules a number of the cells had evidently fallen out, and in these the remaining cells showed a peculiar appearance, being united by spreading protoplasmic processes, some of pyramidal, others of branched form. Some tubules contained coagulated masses, in which were well-stained nuclei. All signs of spermatogenesis were absent. *Microscopic structure of the parovarium:* This consisted of a number of round or oval tubules with wide lumina. Each tubule had a tunic of circularly-disposed smooth muscle-fibres, and internally a single layer of columnar ciliated epithelium. The lumina contained desquamated cells and amorphous material. *Microscopic structure of the small body adjacent to the vas deferens (epididymis)*: This consisted of tubules separated by delicate vascular connective-tissue septa, which passed inwards from the surface. The tubules were round or kidney-shaped in section, and the character of their epithelium varied, in parts being ciliated, in parts being disposed in several layers and forming projections into the lumina. The walls of the tubules contained a layer of smooth muscle-fibres and the lumina were occupied by amorphous substance and desquamated epithelium. Spermatozoa could not be detected.

### *The case of Salén.*

The specimen was demonstrated by Professor Ziegler[1] at a meeting of the German Pathological Society.

Augusta Persdotter, aged 43 years, unmarried. Monthly periods since the age of 17. Passive coitus painful; no active coitus. Feminine habitus. Clitoris penis-like, nearly 5 cm. long, with glans the size of a hazel-nut. Labia majora and minora normally developed. Urethra and vagina open into

[1] 'Verhandl. d. Deutsch. Path. Gesell.,' 1899, S. 241.

the vestibule, the latter by a narrow orifice into which a sound can be passed for a distance of 8 cm. Laparotomy was performed, and a pedunculated cystic fibroid of the size of a man's head removed, castration being performed at the same time. The uterus was enlarged and contained several small fibroids. On each side the Fallopian tube and broad ligament were normal, and a genital gland was present in the usual situation of the ovary. Examination proved that the left gland was a rather small and irregular ovary with Graafian follicles and ova, while the right gland was an ovo-testis, one half consisting of ovarian tissue, the other half of testicular tissue. The ovarian portion was coarsely lobulated, of yellow colour and firm consistence, and under the microscope showed Graafian follicles with quite typical ova, lying in a stroma rich in spindle-cells. The testicular portion was of softer consistence, with a white, polished tunica albuginea. The parenchyma was looser, of brownish-grey colour, and traversed by white fibrous septa; under the microscope it showed tubuli seminiferi lying in an open connective-tissue stroma, presenting collections of interstitial cells, containing fat granules and pigment grains. The tubules were much convoluted and all of about the same diameter. Their membranæ propriæ were mostly thickened and abundantly supplied with concentrically arranged elastic fibres. The epithelium consisted of follicle-cells and Sertoli's cells. Spermatozoa and other seminal cells were absent. The structure showed a striking resemblance to that of the ectopic testis after puberty.

*The case of Blacker and Lawrence.*

The subject was an 8½ months' stillborn fœtus.[1] The external genitals consisted of a small, imperforate, penis-like organ, with a large prepuce; a small orifice at the root of this organ leading into a urogenital sinus, into which opened the separate orifices of the urethra and vagina; and two raised folds of skin, united in a median raphé and resembling the conjoined labia majora. Labia minora were absent. The urethra measured 6·5 mm. in

[1] 'Obstet. Soc. Trans.,' vol. xxxviii, 1896. My acknowledgments are due to the Council of the Obstetrical Society for kindly permitting me to reproduce the details of this case and two of the illustrations accompanying the original paper.

length, and no trace of a prostate gland was present. The vagina measured 8 mm. in length. The uterus consisted of an upper small triangular portion, about 3 mm. in length and breadth, a middle narrow tubular portion 12·5 mm. in length and 1·5 mm. in width and apparently representing the attenuated lower uterine segment, and a relatively large inferior portion or cervix, 11 mm. in length and 6·5 mm. in breadth, presenting a well-marked arbor vitæ. Attached to the right cornu was a Fallopian tube, measuring 2·5 cm. in length, terminating in a fimbriated extremity; connected inferiorly with this tube and mesially with the side of the uterus was the right broad ligament. To the left border of the uterus the left broad ligament was attached, and a fine, thread-like strand was dissected from between its layers at the upper margin, terminating internally in the left angle of the uterus, and externally in a free fimbriated extremity; this strand evidently represented the left Fallopian tube. Imbedded in the left wall of the cervix was a fine tube, which, leaving the cervix near its upper end, passed obliquely upwards and outwards in the left broad ligament and terminated close to the fimbriated extremity of the strand previously mentioned. For the first 2·5 cm. after leaving the cervix this tube had an even calibre; in the remaining 2 cm. it gradually increased in size and at its extremity was remarkably convoluted. The upper convoluted portion was held to represent the epididymis and the remainder of the tube the vas deferens, which was traceable inferiorly within the tissue of the cervix as far as the external os. A genital gland was present on each side. That of the right side had the external appearance of an ovary and was situated immediately below the Fallopian tube, being attached by the whole of its anterior border to the hinder surface of the broad ligament. The gland had an elongated form, with somewhat pointed extremities, and its surface was marked with a few shallow sulci; it measured 12·5 mm. in length and 3 mm. in breadth. From its inner extremity a fold of peritoneum, apparently the ovarian ligament, passed to the right cornu of the uterus, and an ovarian fimbria extended to its outer extremity from the fimbriated end of the Fallopian tube. A small oval body lay between the gland and the tube, in the situation of the parovarium. On microscopic examination the right genital gland was found to be composed of a cellular stroma containing

a number of spaces filled with cells. At the periphery the stroma was thickened and formed a species of albuginea. At one point, in a crypt-like depression of the surface of the gland, some of the superficial epithelium was present in the form of a single layer of cubical cells. The stroma was composed of spindle-cells with oval nuclei. Scattered here and there throughout it were a small number of larger cells of finely granular appearance, irregular outline, and having large nuclei. The cells of the stroma were arranged in a concentric manner around the spaces, but no definite limiting membrane could be detected. The central portion of the gland consisted mainly of stroma, the peripheral part mainly of cell-masses. The cell-masses in the peripheral zone, the largest of which measured $\frac{1}{5}$ mm. in width, anastomosed freely, and from their deeper aspect sent down narrow, slightly tortuous, cell-columns into the central stroma. The columns averaged $\frac{1}{60}$ mm. in width but had no uniform diameter. The cell-masses appeared to consist of two different kinds of cells; most of these were small, round, or polygonal, with a clear, glistening nucleus; the remainder were of similar shape but larger and with a well-stained nucleus, in some instances surrounded by a clear area. At the periphery of the gland the two kinds of cells were indiscriminately mixed; in the cell-columns there was a tendency for the smaller cells to become flattened round the larger, the protoplasm of which became increased in amount; and at the extremities of the cell-columns, in one or two places in each section, the formation of distinct primitive follicles could be observed, a large cell, with its protoplasm further increased in amount, becoming surrounded by a layer of small cells flattened round it. This gland the authors regarded as an ovary. The left genital gland differed markedly from that of the right side. It was oval in shape, and measured 7·5 mm. by 4·5 mm., and presented a small, tongue-like process at its outer end, measuring 1·5 mm. in length. The gland was attached to the hinder surface of the broad ligament close to the outer end of the upper margin of the latter, the tongue-like process being connected with the free end of the Fallopian tube by a fine fold of peritoneum, forming a free crescentic margin between it and the fimbriated extremity of the tube. The external appearance and the microscopic structure of the tongue-like process were identical with the

FIG. 2.

The ovarian portion of the ovotestis of the left side from a human fœtus. There is shown a stroma of spindle-cells arranged in a concentric manner round cell-masses without basement membrane. The cell-masses are arranged in columns of varying diameter and composed of two kinds of cells; most of these are small, round or polygonal, with clear nuclei; the others are larger, with a well-stained nucleus. Towards the periphery (upper part of the fig.) the two kinds of cells are indiscriminately mixed; in the deeper part of the gland there is a primitive follicle containing a large cell or ovum.

EXPLICATIO FIGURÆ.

Ovotestis humani pars feminea. Glandula in duas partes dividitur, quarum alter ovarium, altera testis esse videtur. Pars feminea ex stromate constat in quo adsunt cellularum epithelii collectiones inter se connectæ et e cellulis duorum generum constitutæ. Harum cellularum alteræ parvæ, multiformes; alteræ grandiores sunt. In glandulæ cortice hæc duo genera cellularum sine ordine disponuntur; quibusdam in locis folliculi discerni possunt quorum quisque cellulam grandiorem sive ovum, includit.

appearance and structure of the right genital gland above described; the authors regarded it as an ovary or as representing the external portion of an ovary (Fig. 2). The main portion of the left gland presented a totally different structure. The stroma was of looser texture and contained numerous large irregular cells with well-defined nuclei (interstitial cells), in some places scattered singly through the stroma, in others collected into small masses. Towards the periphery of the gland the stroma appeared to be almost entirely composed of these cells. There was, at the periphery of the gland, a narrow zone of irregular cell-masses which were directly continuous with the more tubular structures found deeper in the gland. These tubules (Fig. 3) were bounded by a distinct limiting membrane composed of a single layer of flattened cells; they were very tortuous, their diameters were uniform, and their boundary lines ran in long curves parallel to one another. In parts of the sections where the individual cells contained in these tubules could be clearly made out, the outermost were seen to be of large size, with abundant protoplasm, polygonal or cubical in shape, placed closely side by side, with a flat base turned towards the basement membrane, and containing large well-stained oval nuclei. Within this outer layer were smaller cells, less closely placed, without definite arrangement, and surrounding isolated cells or a distinct lumen. The only indication of a difference in the character of the cells was that some had nuclei which stained deeply, were homogeneous in appearance, and less highly refractile. In sections made at right angles to the long axis of the gland the tubules could be seen to take a general direction towards the hilum or attached border; here they became greatly reduced in size and formed an ill-defined network or rete, and from this point they appeared to pass out of the gland, but their actual continuation in the mesorchium was not included in the sections made. This, the main portion of the left genital gland, was regarded by the authors as testicular, and the whole gland, including the tongue-like process, they designated an "ovotestis."

This case has been commented on by several authors. Siegenbeek van Heukelom[1] is of opinion that the structures which Blacker and Lawrence regard as seminiferous tubules should be looked upon rather as analogous to the medullary cords

[1] 'Beitr. z. Path. Anat. u. z. allgem. Path.' (Ziegler), Bd. xxii, S. 144.

FIG. 3.

The testicular portion of the ovotestis from the same fœtus. The stroma is of loose texture and contains many large polygonal cells (interstitial cells). In the stroma there are well-defined tubuli furnished with membrana propria and containing epithelial cells, the outermost of which are cubical or columnar in form and with flattened base turned towards the basement membrane. Within this outer layer are smaller cells, without definite arrangement, and within these, again, isolated cells or a narrow lumen.

EXPLICATIO FIGURÆ.

Ovotestis humani pars masculina. In stromate jacent tubuli flexuosi membranâ limitanti circumtecti. Cellulæ in mediis tubulis parvæ, ac sine ordine disponuntur; illæ ad membranam limitantem multiformes aut subcylindricæ sunt, basibus ad membranam pressis. Tubuli quidam lumen ostendunt. In stromate insuper adsunt cellularum collectiones interstitialium.

which are found in the ovaries of many of the lower animals. Adopting the view that the medullary cords of the ovary are homologous with the excretory channels within the testis, Siegenbeek van Heukelom looks upon the tubules present in the specimen as being persistent male excretory ducts; in other words, he considers that not only the vas deferens and epididymis are persistent, but that the intraglandular portions of the ducts also are present. The authors are in full accord with the view as thus stated. Further, he regards that portion of the gland which contains these male channels as being ovarian in nature, but the reasons upon which this opinion is grounded are not mentioned; it is, therefore, impossible to do more than recapitulate the points which have led the authors to an opposite conclusion. These points are: the absence of ova and primitive follicles and of a stroma resembling that of an ovary, the presence of interstitial cells in great numbers, and of a stroma similar to that found in the testis, and the association of these testicular characters with tubules resembling early seminiferous tubules and with a system of canals forming a rete in the hilum of the gland.

Nagel holds the view that Blacker and Lawrence are in error in regarding either of the glands or any part of them as ovarian in nature. He bases this view on the fact that the epithelial elements are still disposed in cell-columns or cell-masses, although a complete albuginea has been formed. "In no stage of the development of the female glands can cell-columns or cell-masses be found which are not separated into primitive follicles, and which are at the same time separated from the surface epithelium by an albuginea."[1] This statement apparently refers to the normal development of the female gland; it is not applicable to a case in which the development of the stroma of the gland has proceeded unchecked, while that of the cell-columns and cell-masses has suffered a partial arrest. An unequal development, such as is here indicated, and which has without doubt occurred in the specimen under consideration, would lead to the anomalous relationship of cell-masses to albuginea to which Nagel has taken exception.

[1] 'Archiv f. Gynäek.,' Bd. 58, S. 86.

*The case of Obolonsky.*

Gabriele L—,[1] aged 12 years, *pensionaire* in a convent, came under treatment for strangulated inguinal hernia and died from peritonitis, which followed the operation. The genital organs were placed in the Pathological Museum of the University of Prague as exemplifying the condition of pseudo-hermaphroditismus masculinus. Twenty years later the specimen was reinvestigated by Obolonsky, who found its state of preservation to be such as to allow of the macroscopic and microscopic structure being ascertained with a sufficient degree of certainty. The external genitals presented the following characters: There was a penis-like organ, 2·5 cm. long, almost hidden between two large folds of skin, which resembled labia majora. This organ was covered with wrinkled skin, which was continuous on either side with the labia and formed a dentate ridge on the inner surface of each; anteriorly the skin formed a prepuce covering a distinct glans. The under surface of the glans was marked by a groove 4 mm. in length and 3 mm. in depth, and at the hinder end of the groove there was a pea-sized prominence towards which the margins of the prepuce converged inferiorly. Two dentate ridges, consisting apparently of mucous membrane, passed backwards from this prominence towards the perineum and bounded a shallow groove 1 cm. in length, into the hinder part of which the urogenital sinus opened by a slit-like orifice measuring 5 mm. from before backwards. The right labium majus was considerably larger than the left, its greater size being due to the presence in it of a mass of fibro-fatty tissue measuring 7·5 cm. by 5 cm. A smooth membrane covered this mass, which was possibly an omental hernia. In the left labium majus there was a hernial sac. Two corpora cavernosa were present, having the normal bony attachments and becoming united above the canalis urogenitalis. Between the cavity of the bladder and the external orifice of the urogenital canal was a tube 4 cm. in length, the upper part of which represented the true urethra and the lower part the urogenital canal. In the hinder wall of this tube and 1·8 cm. from the urethral orifice of the bladder there was a slight prominence—the colliculus seminalis

[1] 'Zeitschrift f. Heilkunde,' 1888, Bd. ix, S. 210.

—which had, in its centre, an opening (the vaginal orifice) of about the size of a hemp-seed; the opening was bounded inferiorly by a crescentic fold. Connected with the hinder aspect of the vagina at its junction with the urogenital canal there was a mass, consisting of cavernous tissue, and apparently representing the bulb of the urethra. The hinder and lateral walls of the urethra immediately above the colliculus seminalis were thickened so as to form a body the size of a hazel-nut; this was found to have the structure of the prostate gland. The vagina measured 6·5 cm. in length and 2·5 cm. in its inner circumference at the widest part, and it was continued superiorly into a uterus unicornis sinister, which in its lower 2 cm. showed well-marked plicæ palmatæ characteristic of the cervix. The uterus consisted of a vertical part, 5 cm. in length, and a horizontally-placed left horn 3·5 cm. in length. On the right side there was a quite rudimentary right cornu. The lining membrane of the uterus was disposed in longitudinal folds which were prolonged into the left horn. The left broad ligament extended downwards towards the left labium majus, in continuity with the hernial sac already mentioned. Imbedded in it was a cord-like structure, which passed from the left cornu towards the hernial sac; it measured 3·5 cm. in length and 4 mm. in thickness, and near the hernial sac it terminated in an oval enlargement 3 cm. in length and 1·5 cm. in width. On section this cord-like structure presented a stellate lumen, along which a sound could be passed as far as the uterine horn, where the lumen became narrowed but could be traced into the cornu itself. Peripherally the canal widened and terminated in a cyst-like dilatation. The lining of the canal and of the dilated extremity presented numerous longitudinal folds. This structure was evidently the left Fallopian tube, as was subsequently proved by microscopic examination. Lying parallel with the Fallopian tube, and having one extremity attached to its cyst-like extremity, was a solid fusiform body measuring 3·6 cm. in length and 5 mm. in thickness. This body was attached to the broad ligament; the peritoneal layer, however, did not form a covering to it but terminated along its base of attachment in a white streak. The body had a smooth surface, and its proximal end was continued into a fibrous strand which was inserted near the extremity of the left uterine horn. Portions of this body

were embedded in celloidin, and sections cut, which presented the following appearances: Externally there was a layer of coarsely fasciculated connective tissue which formed a tunica albuginea. Beneath this was a richly nucleated tissue resembling the cortical layer of the normal ovary, in which peculiar small, mostly rounded, spaces and larger, in many instances bulged, spaces were situated. These spaces contained distinctly recognisable though much altered epithelium, which in some of the bulgings of the larger spaces was still *in situ* and formed a continuous layer. Here and there these spaces contained clear vesicular cells, which as regards their size and their position in the spaces, and the presence in them of round structures resembling germinal vesicles, seemed to correspond to ova, although it was not possible to arrive at a positive conclusion on this point. More centrally the organ presented a loose connective tissue with numerous large blood-vessels. Their microscopic appearances seemed to establish the ovarian nature of the organ without any doubt. The right broad ligament had attached to the outer extremity of its upper border a flattened ellipsoidal body 2 cm. long, 1·5 cm. broad, and ·5 cm. thick, smooth, and polished on the surface. On section this body showed a central fibrous stratum, from the sides of which processes passed off and formed numerous small loculaments which were filled with a loose yellowish tissue. Microscopic examination showed this body to possess an external connective-tissue layer and a parenchyma consisting of closely packed, in places very tortuous, tubules, which contained numerous layers of large, rounded, granular, epithelial cells. The tubules were surrounded by a delicate connective-tissue membrane, and were collected into groups, separated from one another by the fibrous processes previously mentioned. In the larger septa numerous blood-vessels were present. From these appearances it was concluded that the body was the right testicle. A strand passed downwards and inwards from the testicle to the right broad ligament; its lower part was not present in the specimen. On section this strand was found to have a lumen, and the wall of the tube presented internally a mucosa, surrounded by an inner circular and an outer longitudinal muscular layer. The tube was regarded as the vas deferens. Parallel with the free edge of the broad ligament there passed downwards from the testicle another strand

which, from microscopic examination, was considered to consist of a group of coni vasculosi. A third strand passed inwards in the right broad ligament towards the rudimentary right uterine horn; at its outer part about 5 mm. in width, it gradually diminished to the size of a thread internally; its outer end terminated in a fringed extremity. Microscopic examination showed this structure to contain a canal and to consist of a muscular and a mucous layer, the latter forming longitudinal folds in the lumen of the tube. From the inner and middle thirds of this tube a band passed downwards and outwards in the broad ligament, and doubtless represented the ligamentum teres of the right side.

*The case of Schmorl.*

Friedrich W—, aged 22 years, came under the care of Prof. Thiersch in 1887 for the treatment of hypospadias.[1] In 1882 a right inguinal hernia had occurred, reaching to the scrotum. On April 4th, 1887, a first operation was successfully performed, its object being to straighten the curved penis; on May 16th the groove on the under surface of the glans penis was closed; and on August 1st closure of the groove beneath the body of the penis was effected. In connection with the first operation catheterisation was employed, but, although the catheter passed readily, no urine was obtained, and an injection of salicylic solution was followed immediately by swelling of the left groin. On the following day a catheter was successfully passed into the bladder, and 1200 c.c. of urine evacuated. At the time of the third operation also a catheter was passed without difficulty, but, as on the former occasion, no urine was obtained, and an injection of salicylic solution caused a swelling in the left groin as before. On recovering from the anæsthetic the patient complained of pain in the left groin; vomiting commenced and subsequently fever, and the parts around the swelling became reddened. On August 6th the swelling was incised, and a body resembling an atrophied testicle removed from the inguinal canal close to the internal abdominal ring. Death occurred on August 7th.

The patient was of male habitus, with somewhat high-pitched

[1] 'Virchows Archiv,' 1888, Bd. 113, S. 229.

voice. The muscles were slightly developed and the skin delicate. The skull was of the male type, and the frontal eminences well marked. The upper lip, chin, and cheeks were covered, but not thickly, with hair, reaching a length of 2 cm. The thyroid cartilage was only slightly prominent. The breasts were undeveloped, and the nipples small. The pelvis approached more nearly the female type, and had the following measurements: Distantia spin. ant., 25·5 cm.; distantia crist., 27 cm.; distantia trochant., 29·5 cm.; conjugat. ext., 18·7 cm.; conjugata vera, 11·3 cm.; diam. trans., 12 cm.; diam. obliq. sin., 11·7 cm.; diam. obliq. dex., 11·7 cm. The hands and feet were small and delicately formed. The pubic hair terminated superiorly in a well-defined line, and a mons veneris of the female type was present, below which was a penis measuring (after the operation for straightening) 5·5 cm. along the dorsum, 4·5 cm. along the under surface, and 8 cm. in circumference. There was a well-developed glans, devoid of a prepuce and without a urethral orifice; on its under surface was a groove which was continued along the under surface of the body of the penis, and ended in an oval aperture ½ cm. in length, bounded by two small folds of skin, which became united posteriorly. Partly overlapping the penis laterally were two folds of skin resembling an imperfectly developed scrotum. These folds commenced posteriorly as a slight prominence in front of the anus, presenting a median raphe. The right fold was somewhat larger than the left, and contained a firm elongated structure with a lobulated surface, which proved to be omentum; the left fold contained no solid body. In front of the right external abdominal ring there was a firm body of elongated oval form and of the size of a small plum, from the outer end of which a cylindrical cord was traceable into the inguinal canal. The body previously mentioned as having been removed from the left inguinal canal also presented a cord-like strand which passed from it into the abdomen. The urethra measured 7 cm. in length and opened at the orifice situated at the root of the penis; its upper part was surrounded by a body resembling a prostate, measuring 2 cm. in diameter, which, however, contained no glandular tissue but was composed chiefly of smooth muscle-fibre. On either side of the membranous part of the urethra was a corpus cavernosum urethræ; these diminished in size anteriorly, where they lay in apposition

to the well-developed corpora cavernosa penis. Situated in the hinder wall of the urethra, at a distance of 3·5 cm. from the external orifice, was a triangular opening 4 mm. in width; a sound could be passed upwards and to the left through this for a distance of 15 cm. into a tubular structure which corresponded to the vagina and uterus. This structure was supported by a median peritoneal fold (broad ligament), which was attached anteriorly and posteriorly to the bladder and rectum respectively; its length was 15·5 cm., its thickness $\frac{3}{4}$ cm., and its breadth varied at different parts, but gradually increased in size from below upwards. It was marked off by a circular groove into an upper uterine and a lower vaginal portion. In the latter the mucous membrane resembled that of the vagina, and showed indications of columnæ rugarum. The upper division presented an inferior thick-walled cervical part, 4 cm. in length, with distinct plicæ palmatæ, and an upper part 6 cm. in length, the cavity of which was triangular in form and narrowed superiorly into right and left horns, the latter of which was drawn out in the direction of the left groin. The left cornu was continued as a strand having the thickness of a crow-quill, which, on section, presented a stellate lumen, and which passed into the left inguinal canal and joined the structure which was removed in the last operation. This structure measured 5 cm. in length and 2 cm. in breadth and resembled an adult testis; on microscopic examination it was found to consist mainly of convoluted tubes. Below the inner end of the hollow strand (Fallopian tube) there was a body of the size of half a cherry-stone, one surface of which was rounded whilst the other was evidently a surface of section; it was therefore apparently part of a larger body, the remaining portion of which, however, could not be found, and was probably lost at the time of the operation or at the autopsy. This body, which was regarded by Schmorl as part of an ovary, had the following microscopic structure: Its surface was covered with a single layer of short cylindrical epithelial cells, which in places formed crypts in the surface of the organ, in some cases empty, in others filled with cells. Beneath the epithelium was a narrow, scantily nucleated layer composed of elongated connective-tissue cells. This layer passed without definite demarcation into a zone consisting of numerous round and large spindle-shaped cells with relatively large elongated nuclei, the cells being arranged mostly

in thick, wavy bundles. In this zone there were "cell-globes," mostly somewhat elongated and composed of cells of large size and rounded form, with bright granular protoplasm and large, clear, vesicular nuclei in which a single nucleolus was present. Fine processes of the surrounding spindle-cells could be traced between the individual cells in some of the cell-globes. This zone also contained round and oval cell-nests composed of small, closely-packed epithelial cells; the peripheral cells had a short cylindrical form, but no membrana propria was present. Finally, there were in this zone a few large round and oval spaces lined with low cylindrical epithelium. These structures were surrounded by a well-defined layer of concentrically arranged spindle-cells, and they contained a finely granular mass with scattered desquamated cells and free nuclei, but no large cells resembling ova. In the deepest part of the organ the tissue was more open, less cellular, richer in fibrous and elastic elements, and contained large veins and numerous thick-walled and convoluted arteries. The right uterine horn was continued into a solid cord of the thickness of a knitting-needle, which crossed in the upper edge of the broad ligament to the right inguinal canal, and after becoming considerably enlarged, joined the body situated at the external abdominal ring. This body consisted of three structures. One of these retained its connection with the peritoneum, and ended in a slight swelling at the fundus of the processus vaginalis (*lig. rotundum*); the second part was tubular at its extremity, and had a funnel-shaped orifice surrounded with fimbriæ (Fallopian tube); the third structure consisted of a genital gland, 2·5 cm. in length, and 1·75 cm. in breadth and thickness. The gland had the configuration of a testis, and was smooth and polished on the surface; it was formed of a firm fibrous albuginea, from which narrow trabeculæ passed inwards into a parenchyma of fine tubules, recognisable to the naked eye. The tubules converged towards the attached edge of the organ. Microscopic examination confirmed the view that this organ was a testis, but no spermatozoa could be found, and both epididymis and vas deferens appeared to be absent. In a thin membrane situated between the Fallopian tube and the fundus of the processus vaginalis six narrow tubules were present, and probably represented the parovarium.

The absence of Heppner's case [1] from the above series may call for remark, and, without denying that it may be a case of true hermaphroditism, one may briefly mention the reasons which seem to justify a suspension of judgment. The subject being an infant, it was especially necessary that the microscopic structure of the genital glands should be described and illustrated with fulness and precision. It cannot be said that the illustrations accompanying Heppner's paper fulfil this requirement. More particularly, the figure of the microscopic structure of the so-called testes fails to produce any conviction as to the true nature of the organs. No reference is made to the presence or absence of the epididymis, and the possible relation of the two bodies to this structure is not discussed.

*May 16th*, 1905.

[1] 'Archiv f. Anat. u. Physiol. u. Wissenschaft. Med.' (Reichert und Du Bois Reymond), 1870, S. 679.

## 3. *Opsonic content of the serum in the course of acute pneumonia.*

By G. G. Macdonald.

In a series of papers published in 1903–1904 by Wright and Douglas it is demonstrated that in the course of many infections there is a substance present in the serum which attaches itself to the invading bacteria and thus renders them suitable pabulum for the phagocytic property of the polymorphonuclear leucocytes. This substance they designate "opsonin." During the process of active immunisation against staphylococcus, micrococcus melitensis, bacillus tuberculosis, etc., they have been able to show that for these infections the opsonic content of the serum is increased, and have thus demonstrated that in addition to antitoxic and bactericidal immunity there is a third type—opsonic immunity—brought about by a coalition and interaction of the body humours and cells.

Recently, in the examination into the phenomena of the immunity acquired in passing through an attack of acute croupous pneumonia, I made an investigation into the course of the opsonic content of the serum during this disease.

Fifty-five cases were at my disposal, twenty-five of these more or less typical cases of acute croupous pneumonia; nine others were in children with the clinical diagnosis of acute croupous pneumonia, seventeen cases were definitely broncho-pneumonia, and the remaining four were cases of post-pneumonic empyemata from which the pneumococcus was isolated in more or less pure culture.

The technique employed was that of Wright and Douglas. Three parts of the serum of the patient were added to three parts of my own citrated and washed corpuscles and an emulsion of pneumococci. These were thoroughly mixed and incubated at body temperature for fifteen minutes. Films were then made of the contents of the mixing pipette, dried and stained by Leishman's dye. The number of pneumococci in thirty to fifty polymorphonuclear leucocytes were counted and an average per leucocyte determined. Simultaneously with each experiment a control, or series of controls, was made with the sera of normal healthy individuals. The result is expressed in terms of the "opsonic index," the average number of cocci per polymorphonuclear leucocyte when the serum added is that of a

normal individual being regarded as unity, and the opsonic index of the pneumonic patient is expressed in relation to the normal opsonic index of a healthy person.

The strains of pneumococci used in these experiments were seven in number, being isolated from empyemata and other pneumococcal conditions, and many of them were employed a few days later in testing the sera of the patient from whom they were isolated. All the strains reacted similarly to variations in the opsonic index. The great essential in the preparation of the pneumococcal emulsion is the securing of homogeneity. One strain of pneumococcus had to be discarded owing to the cocci adhering together in clumps, and was therefore quite unsuitable for the determination of the average number of cocci in a number of leucocytes. The best means of attaining uniformity is to thoroughly shake up the emulsion and then centrifugalise for a few minutes. The masses and clumps are then deposited and the uniform upper layer of emulsion employed in the tests. The cultures were twenty-four hours old; in no case were cultures older than forty-eight hours used. The culture medium employed was glycerine-agar.

Of the twenty-five cases of acute croupous pneumonia fifteen were examined regularly from day to day throughout the course of the disease, and the opsonic index of the serum determined before, during, and after the crisis. In the other ten cases it was only possible to obtain the serum at less frequent intervals, but the results in those in no case disagreed with the opsonic curve determined for the others.

It will be convenient to discuss the relation of the opsonic index to:

(1) The chill period.

(2) The course of the disease.

(3) The final result, whether going on to rapid or tardy resolution, to a fatal issue, or to complications.

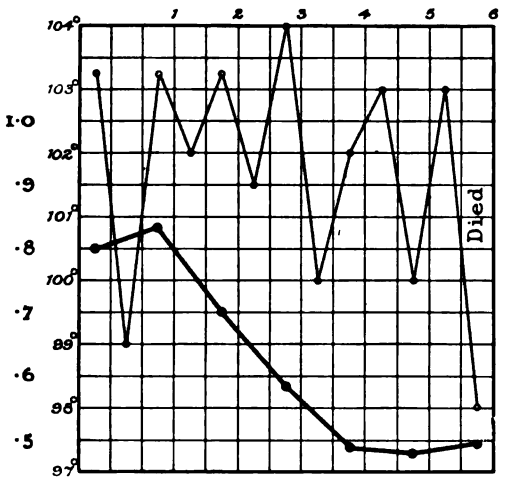
(1) At the chill period we have only been able to examine the serum of one patient. This was obtained two hours after the initial rigor, while the patient was feeling very cold and shivery. The opsonic index stood at ·65; the original index was unknown, but in a healthy girl such as the patient was probably near that of a normal person.

(2) During the evolution of the disease the opsonic index of

the disease is considerably below unity, affording indices varying from 0·45 to 0·8. The lowest index observed was 0·45, in a poor, under-nourished woman, who rapidly succumbed. In fact, all the cases in which the opsonic index fell below 0·5 terminated fatally. Considerable daily variations are present in the development of the disease. A progressive fall in the opsonic content of the serum does not seem invariably to indicate a fatal issue, though such a fall was observed in most of the fatal cases (see Chart I).

(3) On the incidence of the crisis the greatest changes take

CHART I.

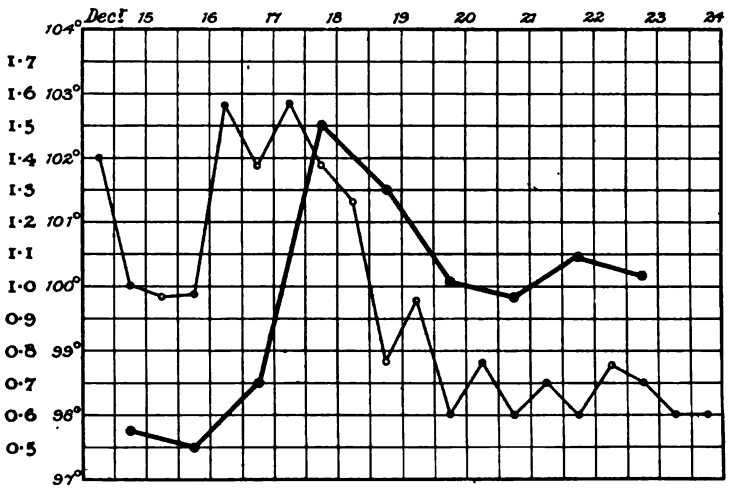



**A fatal case of pneumonia. The thicker line and numbers represent the opsonic curve; the other, the temperature.**

place in the opsonic index. For some twelve hours the amount of opsonin in the serum is vastly increased and with the increase the patient's condition seems to improve very greatly, and the critical phenomena occur. The amount of opsonin began to increase before any fall in the temperature was noticeable in many cases in which, with a high temperature in the morning, but a normal or higher opsonic index, one could almost predict the critical fall to take place during that day. A pseudo-crisis is not associated with increase in the opsonic index.

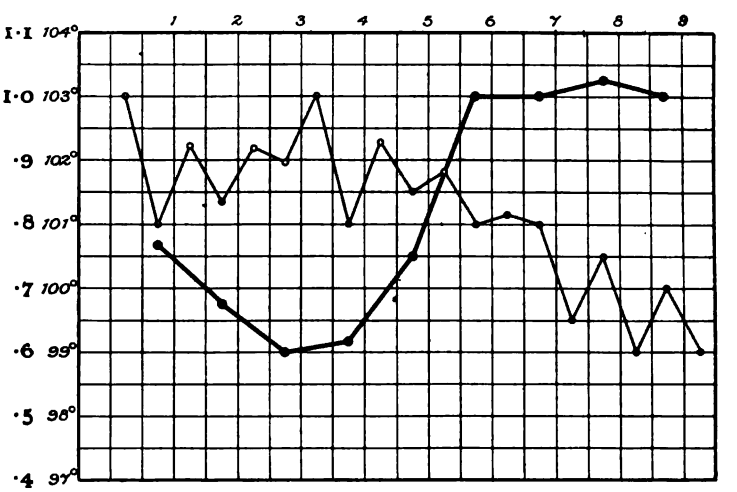
In cases undergoing rapid resolution the opsonic index rises suddenly to above normal, reaching 1·1 to 1·6. When the resolution is more tardy in nature, the rise is, as a rule, not so

CHART II.




From a case of pneumonia undergoing rapid resolution. The thicker line and numbers represent the opsonic curve, the other that of the temperature. The opsonic index rises above the normal, and falls to normal two days after the crisis.

CHART III.




From a case of pneumonia undergoing gradual resolution, and showing the gradual rise of the opsonic index (indicated by the thicker curve) to unity.

high, but a slight increase to the normal comes on and persists, the temperature and the general condition improving gradually a day or two later (Charts II and III). In the cases of rapid resolution the index again falls to normal in periods varying from one to three days.

In fatal cases the opsonic index goes on diminishing till the *exitus lethalis*. This was constant in the five cases with fatal issue. In one case the temperature fell to normal, after a typical pneumonia, but the opsonic index did not rise. He died on the following day.

Of complicated pneumonia I have examined two cases of empyema, one of meningitis, one in which the opposite lung was attacked after the first crisis. The meningitis case died in three days with falling opsonic index. (The pneumococcus was isolated from the cerebral membranes *post mortem*.) One of the empyema cases died, the other survived. In the fatal case the pneumonia seemed to crisis, but not satisfactorily, for two days later the opsonic index rose, and continued rising; the pleural cavity was then aspirated and a large quantity of pus withdrawn (grew pneumococcus). In spite of this the patient died with an index above normal. In the other case the opsonic index rose to 1·5, but on opening the pleural cavity it fell to normal and healed quickly.

The amount of opsonin present in the serum and exudate in post-pneumonic empyema was examined in four cases. Case 1 gave an opsonic index of 1·4. Twenty-two ounces of pus were aspirated from his chest (gave pure culture of pneumococcus). The opsonic index of the liquor puris compared with the blood serum was 0, the leucocytes refusing to pick up a single coccus. Two days later the empyema was drained; the blood-serum at time of operation had opsonic index of 1·35, and the liquor puris of the exudate 0·5. Next day that of the serum was 1·37, and of the exudate 1·36. The progress of the case was rapid, the opsonic index of the serum and fluid of the exudate were tested successively for ten days, and both adjusted themselves gradually till both were approximately normal. The exudate always gave a slightly lower reading than the blood-serum. The blood-serum of Case 2 gave an opsonic index of 1·1 on the day subsequent to draining operation on his pleural cavity, while the exudate gave an index of 0·99. The infection was a pure

pneumococcus one, and the discharge ceased within a week. Case 3 was a child, and fatal. Along with pneumococcus, *Staphylococcus albus* was present. Two days before death opsonic index of the serum was 1·2, and that of the exudate 0·3. Case 4 had a discharging empyema subsequent to pneumonia for two years. The organisms isolated were *Bacillus coli, Staphylococcus albus*, etc. The opsonic index of the serum of the blood was 0·55, and that of the discharge 0·52. Treatment by continuous negative pressure was continued for two months, during which he improved greatly. At the end of the time the opsonic indices in the blood-serum and exudate fluid were 1·08 and 0·85 respectively.

The seventeen cases definitely diagnosed as broncho-pneumonia came from the children's wards. These were similarly tested with pneumococcus and their indices determined. The results in these cases are very much less definite than in genuine croupous pneumonia in adults. In some of the cases with a high temperature and signs of a severe infection the opsonic index was normal throughout. In most of the cases the results are so varying that a definite curve for the course of opsonin in this affection could not be attempted. Of the nine cases in children diagnosed clinically as acute croupous pneumonia, three gave charts very similar to those of adults; the others were more or less irregular.

*The significance of the variations in the opsonic content in the serum in acute pneumonia.*—In the majority of patients suffering from staphylococcic infections, as furunculosis, sycosis, acne, etc., or tuberculous infections, as phthisis, lupus, Addison's disease, etc., the opsonising power of the serum has been found to be below that of a normal individual. The same is true of pneumococcal infections and in the pre-critical period of acute pneumonia. The critical changes in the course of pneumonia must be regarded as phenomena of immunisation. From the nature of the opsonin it is manifest that, with the rise in the amount of opsonin in the serum, and accordingly in the serum bathing the leucocytic exudate in the pulmonary alveoli and capillaries, more pneumococci are prepared for the leucocytic meal, and they are taken up in greater number, the intoxication of the individual rapidly ceases, and the disordered metabolism is swiftly restored.

Should, however, the amount of opsonin in the serum fall

instead of rise, the quickly proliferating cocci are not taken up in such numbers by the phagocytes; the pulmonary alveoli and capillaries thus contain many free cocci, a condition of bacteriæmia results, and with an aggravation of this condition intense intoxication and death.

In the case of empyema developing from pneumococcal pleuritis, the numerous cocci present and proliferating between the layers of pleura absorb all the opsonin from the exudate effused. On opening such a pleural cavity fresh serum laden with opsonin is poured out into the cavity, the cocci are taken up rapidly by the leucocytes in the granulating zone and exudate and destroyed. The condition, therefore, tends to go on to healing should the opsonic content of the serum be sufficiently high. If it be low, it is manifest that the serum poured into the opened pleural cavity would also be low, the cocci would be less efficiently picked up by the leucocytes, and the disease would tend to continue for a longer period and become an essentially chronic discharging empyema.

Analogous cases are tuberculous and staphylococcic abscesses, in which, as Wright and Bulloch have demonstrated, the fluid of the pus of a closed abscess possesses no opsonic power, although the blood of the patient exhibits it in a considerable measure. If these be opened, the lymph afterwards flowing from the wound has high opsonic power.

The high opsonic index registered in cases of closed empyemata may be regarded as an expression of immunisation from resorption of immunising products from the pleural cavity. When opened and the conditions favouring resorption removed, the opsonin in the serum is restored to normal in a shorter or longer period.

That the variation in opsonin in acute croupous pneumonia is a specific variation for the pneumococcus is shown by testing the opsonic content of the blood for another bacterium—*e. g.* the staphylococcus. Thus it is shown that while the pneumococcal opsonin undergoes great changes in quantity during the course of acute croupous pneumonia, the opsonic content for staphylococcus varies from the normal in only a slight extent. Several of the cases were tested throughout, and in each case this was verified. Thus, one day three patients gave indices for pneumococcus of 0·5, 0·65, and 0·95, and staphylococcus 1·09, 0·85, and

1·0 respectively. Two days later the same cases were tested for both organisms, giving indices of 0·85, 1·3, and 1·03 respectively, while the staphylococcic indices were 1·0, 0·86, and 1·01 respectively.

Another method of demonstrating the specificity of opsonin in the serum is by an absorption experiment. Serum is taken and the mixture digested with a measured quantity of thick pneumococcal emulsion in normal salt solution for fifteen minutes at 37° C. A similar measured quantity of normal saline solution is added to the control. The cocci are then removed by centrifugalisation and the supernatant fluid tested against the control. The result is: Control for pneumococcus, 1·00; supernatant for pneumococcus, 0·12; control for staphylococcus, 1·00; supernatant fluid for staphylococcus, 0·95. The remainder of the supernatant fluid is divided into two equal parts, and a quantity of thick staphylococcus emulsion added to one while an equal quantity of saline is added to the other half. Both are digested for fifteen minutes at 37° C. The cocci are deposited by the centrifuge. The supernatant fluid is tested with pneumococcus, staphylococcus, and tubercle bacillus.

| | For Pn. | For Staph. | For T. B. |
|---|---|---|---|
| Opsonic content of control . . | 1 | 1 | 1 |
| „ „ supernatant fluid | 0·10 | 0·13 | 0·76 |

From these experiments it may be deduced that there is an opsonin specific for each organism or group of organisms (the opsonin for *Staphylococcus aureus* does not seem to be different from that of *Staphylococcus albus*), and the changes in the opsonic content in a particular infection concern only the opsonic content with reference to the infecting agent.

No constant relation between the degree of leucocytosis and the amount of opsonin in the serum could be traced either in the course of acute pneumonia in man or in animals infected with the pneumococcus. The leucocytosis is the cellular reaction product of the organism on infection, the changes in opsonin part of the humoral reaction.

I am much indebted to Dr. Bulloch, of the London Hospital. for much advice and help, while working in his laboratory, on the subject during the year 1904.

*November*, 1905.

## 4. *Gonococcal endocarditis.*

By T. J. Horder.

The gonococcus has been cultivated from the blood during life in about a dozen cases. The first recorded instances of successful blood-cultures in gonorrhœal septicæmia were by Thayer and Blumer in 1896 and by Ahmann in the same year. Ahmann's patient was suffering from multiple arthritis; Thayer and Blumer's patient was suffering from endocarditis. Six other cases of gonococcus endocarditis have since been diagnosed by means of blood-culture, the most recent being one reported in the 'Boston Medical and Surgical Journal,' July 28th, 1904, by C. F. Withington, which is of special interest in that at the time of the report the patient was stated to have almost recovered from his disease. A list of the hitherto successful gonococcus blood-cultures appeared in the 'Johns. Hopkins Hospital Bulletin' for October, 1902, where a case of gonorrhœal endocarditis is described by Harris and Johnston. No case in which the gonococcus has been cultivated from the blood has hitherto been recorded in this country. I have lately obtained good cultures of the gonococcus from the blood of a patient admitted to St. Bartholomew's Hospital. The blood was examined upon two separate occasions, with positive results.

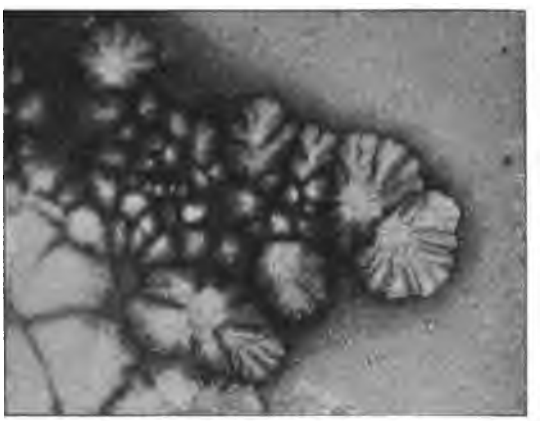
The patient, James H—, aged 21 years, came under observation on May 9th, 1904, as a case of typhoid fever. The occurrence of a markedly intermittent temperature, however, together with a systolic heart murmur and an enlarged spleen, led to his examination by blood-culture. When the organism obtained was found to be gonococcus the patient was questioned as to the occurrence of gonorrhœa and gave a history of the primary infection three and a half months previous to admission. He also stated that one and a half months previous to admission he had kept his bed for a few days with pain and swelling in the left knee-joint, which his doctor had informed him was due to gonorrhœa.

*Blood-culture.*—This was undertaken twice, at intervals of twelve days.

*First culture, May 12th.*—The technique employed was similar to that described in the succeeding article on influenza endocarditis (*q. v.*). No growth appeared during the first twenty-four hours. On the third day, however, many very small, powdery

colonies were seen in the four broth-tubes used. The growth took place as readily in the tubes containing much blood as in

FIG. 4.



Colonies of gonococcus on blood-agar; fourth day. × 40.

FIG. 5.

A colony of gonococcus on blood-agar, showing a highly crenated form; seventh day. × 40.

those in which the blood was considerably diluted. On the surface of two agar-tubes two or three colonies appeared close to the mixture of blood and condensation fluid on the third day. They were somewhat translucent, scarcely raised above the sur-

face of the medium, and possessed very irregular edges (Fig. 5). In five days the colonies in broth were about as large as ordinary pin's heads. Films from the broth and agar colonies showed a large coccus, chiefly, but by no means entirely, in the form of diplococci, staining feebly by Loeffler's blue, well by dilute carbol-fuchsin, and losing Gram's stain readily. All the preparations showed great differences in size of the individual cocci, a feature which seems to be very characteristic of the gonococcus in culture. Differences in the intensity of staining were also a feature of the films. But a reniform appearance was never met with. Subcultures on agar, serum-agar, and serum failed to grow, but on blood-agar plates good growth appeared in twenty-four hours. At first the colonies on plate cultures were almost regular in outline, tending to coalesce. They were much more vigorous and numerous on the parts of the plate where the blood was plentiful than elsewhere. About the third day the edges of the colonies showed some irregularity, which became progressively more marked, until at the end of a week the amount of indentation was very striking. A flourishing colony at this time measured 4 mm. in diameter.

*Second culture, May 24th.*—Upon this occasion the blood was poured directly on to four agar-plates as well as into three broth-tubes. In forty-eight hours many small colonies appeared upon all the plates, having characters similar to those obtained in previous subcultures. Films also showed the same features as before. With this second growth, however, subcultures were obtained on ordinary agar, on glycerin agar, and in broth. Second subcultures failed in all these cases unless blood were added to the media. No growth was obtained on gelatin slopes, but a feeble growth occurred, with uniform turbidity, in melted gelatin.

The cultures and the films compared exactly with those obtained about the same time from the pus of a gonorrhœal knee-joint occurring in another patient.

Pathogenicity was tested in several ways, but always with negative results. A mouse and a guinea-pig were both inoculated intra-peritoneally with large doses of original blood-broth cultures. The guinea-pig received two whole broth-tubes, amounting to nearly 10 c.c. of the culture. Three large guinea-pigs were inoculated *per urethram* with the original vigorous culture of the organism, but without any effect.

The clinical details of the case are here omitted. It may be stated, however, that after the result of the blood-culture was known the patient's urethra was searched for the presence of gonococci but without finding any. The *leucocyte count* is of interest: May 5th, 22,000; May 17th, 21,500; May 24th, 12,000; May 27th, 9200; June 2nd, 9200; June 8th, 11,500; June 9th, death.

The high leucocytosis at the time of the patient's admission is thus seen to have gradually diminished with his loss of resistance; a terminal increase occurred just before death, which was preceded by signs of kidney failure and of extensive consolidation of the right lung.

*Post-mortem examination.*—Made twenty-four hours after death. A few petechiæ were seen over the chest and arms. All the organs were somewhat œdematous. The right lung was completely consolidated, giving the usual naked-eye appearances of early lobar pneumonia. On section the microscope showed very little fibrin and few mast-cells in the alveoli; much of the consolidation appeared to be due to œdema. The apex of the left lung was similarly affected.

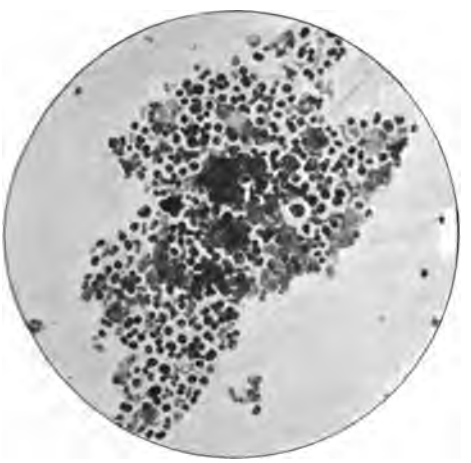
The *spleen* weighed 22 oz. and measured 10 inches in its longest diameter. At about its centre was a large infarct which had undergone considerable cicatrisation. Microscopically there was no recent infarction, and there was no evidence of any organisms being present. The *kidneys* weighed 8 oz. each, were large, very pale, with mottled surface. On section the cut edge showed the cortex swollen and somewhat everted. Examined microscopically, there was seen to be considerable and recent infiltration of round cells between the tubules lying beneath the capsule, some acute inflammation of the glomeruli and peri-glomerular tissue, and some tubular degeneration.

The *heart* weighed 16 oz. The myocardium was natural. All the valves were natural except the mitral, the cusps of which were thickened and were the seat of two large vegetations, of putty-like consistency, projecting into the orifice of the valve. These masses were opaque, light yellow in colour, granular, and on pinching one of them with forceps for purposes of cultivation, the material came away easily and crumbled. The vegetations had no ragged or fungating character. There was no destruction of valve or myocardial tissue.

*Bacteriological examination.*—Rubbings from the vegetations on coverslips yielded large numbers of non-Gram-staining cocci, many of which stained feebly. No Gram-staining organisms were present.

A section through the *mitral valve* and one of its vegetations showed the cocci disposed in a series of linear masses just beneath the superficial fibrinous layer of the tissue. They did not invade the deeper tissues of the valve. This accords with the ease with which one of the vegetations came away in the

FIG. 6.



Gonococci in film preparation, from a blood-agar plate, showing so-called involution forms; fourth day. Stained with dilute carbol-fuchsin. × 1000.

FIG. 7.

Section of mitral valve affected with gonococcal endocarditis. × 85.

*post-mortem* room, leaving an endocardial base which scarcely showed any loss of surface.

The heart's blood was sterile. A piece of the vegetation smeared over a blood-agar plate gave about half a dozen small colonies of gonococci on the general surface of the medium, and a group of thickly studded colonies of the same organism immediately around the spot where the bit of tissue lay. Films from these colonies confirmed the *post-mortem* diagnosis of gonococcal endocarditis. Cultures made from the spleen were sterile.

*April* 18*th*, 1905.

## 5. *Bacillus influenzæ as a cause of endocarditis.*

By T. J. HORDER.

I HAVE recently cultivated the influenza bacillus from the blood of two patients who were at the time of the examination suffering from that form of endocarditis which is clinically termed "malignant," "ulcerative," or "infective." In each case this bacillus was the only organism obtained in the blood-culture; in one case the blood-culture was undertaken upon four, and in the other case upon two, separate occasions. In all six instances the result was positive and of the same nature.

Both cases were fatal. In the first case the diagnosis was arrived at by means of the blood-culture as long a time as six weeks before death; in the second case the nature of the disease was discovered in the same manner five weeks before death.

*Post mortem*, the diagnosis was verified in both cases; the endocardial vegetations gave a growth of influenza bacilli, and sections through the endocardium showed this same organism invading the tissue deeply and in large masses. Neither in the cultures nor in the sections could any other organism be demonstrated.

The organism obtained *ante* and *post mortem* had all the characters of the influenza bacillus as described by Pfeiffer, Canon, Kitasato, and Klein. A short, non-motile bacillus, with rounded ends, tending to show considerable variation in size and shape; bipolar staining is common, suggesting, when marked, a diplococcus; Gram's stain is quickly and invariably lost; staining by ordinary dyes is feeble, but dilute carbol-fuchsin gives good results. Growth only occurs in the presence of highly-organised proteid matter, blood and hæmoglobin giving the best results. A first subculture without blood may grow on agar or glycerine agar, or in broth, but rarely a second subculture, unless fresh blood be added; no growth occurs on gelatin. The bacillus is a strict aerobe—no growth is obtained in an atmosphere deprived of oxygen. Growth on blood-agar appears during the first forty-eight hours as minute, discrete, translucent, dew-drop-like colonies; they are raised and sharply outlined, but they often escape attention if not carefully looked for by reflected light, so that shadows are produced. Growth only occurs at a temperature near to that of the human

body, and the culture dies quickly if not often transplanted. The ordinary animals of the laboratory are immune: no pathogenic effects are obtainable in mice, guinea-pigs, or rabbits, whether the inoculation be made subcutaneously, intra-peritoneally, or, in the case of rabbits, intravenously.

The organism obtained in the two cases now dealt with was, for a specimen of influenza bacillus, exceptionally vigorous. This probably explains some points in which it was found to vary from the classical features just quoted. The first growth direct from the blood on to solid media gave colonies which were sometimes of considerable size and more or less opaque. They were noticed to be viscid in consistency, the platinum wire bringing away the organisms in a stringy mass, which only made a uniform emulsion after much rubbing up in the water used to prepare the film. If the growth in the condensation fluid were used to make films, this same difficulty was also experienced. The first subculture grew well, especially on glycerine-agar; a second and even a third subculture was often obtained without the addition of blood or hæmoglobin. By the addition of a little blood dying cultures could always be revived. In one instance this occurred in a culture a month old, a much longer time than is stated to be possible by Pfeiffer and others. These later cultures, however, always consisted of translucent colonies; they were never opaque. Several times growth of first and second subcultures was obtained in melted gelatin. In broth the usual appearance was that of a powdery deposit at the bottom of the tube. A striking morphological feature of the organism was the occurrence of long bacilli, measuring several $\mu$ in length, resembling the threads seen in some typhoid cultures. Another characteristic was the arrangement of the bacilli in groups in which the individuals lay in twos and threes, close and parallel to each other. The organism was never noticed to grow in chains. As these blood-cultures yielded a very abundant growth of the organism, it was possible to inoculate animals with large numbers of the bacilli. This, together with the exceptional vitality of the organism, makes the negative effect of the inoculations a striking confirmation of all previous observations on this point.

Case 1.—Walter B—, aged 31 years, admitted to St. Bartholo-

mew's Hospital on May 14th, 1904, suffering from aortic regurgitation, with quotidian intermittent fever.

*Blood-culture.*—Undertaken upon four occasions. In each instance the same technique was employed. One c.c. of sterile sodium citrate was drawn up into a 5 c.c. sterilised glass syringe, and a vein at the bend of the elbow was punctured after sterilisation of the skin. The syringe was allowed to fill with blood. Four broth-tubes and two sloped agar-tubes were then inoculated with the blood, different amounts of the blood being used in each of the broth-tubes. These different dilutions were made on account of theory and in conformity with custom, the idea being that in the tubes with little blood and much broth any antibodies present which might inhibit growth of the organism would be diluted; whereas in the tubes with much blood and little broth growth of the organism would occur more surely if it were only present in the circulation in small numbers. In the actual results, however, no difference was obtained in the two sets of culture-tubes. There would seem to be little or no bactericidal power in blood for the influenza bacillus. This is in accord with the facts already stated with regard to the cultivation of the organism outside the body. After rapidly rolling the inoculated tubes between the hands they were kept absolutely still in a vertical position in the warm incubator (37° C.), and any shaking of the tubes was carefully avoided during later examinations. Previous experience in blood-cultures had shown that in this way it was possible to obtain a colourless jelly-like clot, which remained suspended in the broth and formed an excellent nidus for the development of any colonies. The hæmoglobin usually sank to the bottom of the tube in the course of the first twenty-four hours.

*First culture, May 26th.*—On the second day small colonies were seen in the clot of the broth-tubes, and near the mixture of blood and condensation fluid of the agar-tubes. The colonies in broth were opaque and white; on agar they were also opaque, circular, well raised, with clear outlines. The growth in broth was much more abundant than on the agar surface. There were about nine or ten colonies in each c.c. of blood. The colonies in broth and in the agar condensation fluid were tough and stringy, difficulty being experienced in making uniform films from them. The surface colonies in agar were also somewhat viscid, but

yielded good films. The organism was a very minute bacillus, about ·75 to 1 $\mu$ in length, non-motile, staining feebly with Loeffler's methylene blue, rather better with dilute carbolthionin, but very well with dilute carbolfuchsin (1 in 10). Gram's stain was readily lost. Some of the bacilli showed a degree of bipolar staining; others resembled cocci rather closely. The individual members never grew in true chains. The resemblance to *B. influenzæ* was morphologically so close that, in conjunction with

FIG. 8.

*B. influenzæ* in blood-culture. First culture in Case 1. Colonies in clot of the broth-tube; third day.

FIG. 9.

*B. influenzæ* in blood-culture. Fourth culture in Case 1. Numerous colonies in the clot of the broth-tube; third day.

the above-named cultural and staining features, the opinion was expressed that this was the organism which had been isolated.

Drs. Klein and Andrewes were good enough to examine several of the films; they also expressed the opinion that the organism was the influenza bacillus. A couple of films were sent to Prof. Pfeiffer, who confirmed this view.

Subcultures verified the conclusion arrived at. Growth was very scanty upon ordinary agar, better upon glycerine-agar. The colonies were very small, quite transparent at first, becoming

slightly opaque after four or five days. In broth during the second twenty-four hours slight turbidity occurred, with a powdery deposit at the bottom of the tube. Second subcultures either grew very feebly or not at all. The addition of a little blood to the medium, however, caused again a fairly vigorous growth. No growth was obtained on gelatin in the cool incubator (22° C.), but there was some growth in melted gelatin (37° C.) at the first subculture. Films made from subcultures showed more definite bacillary forms than in the case of the original cultures. It was in the subcultures, also, that the elongated forms previously mentioned occurred. No pathogenic effects were ob-

FIG. 10.

*B. influenzæ.* Film from original blood-broth culture; three days old. × 1000.

FIG. 11.

*B. influenzæ* in blood-culture. First subculture on glycerine-agar; four days old. × 1000.

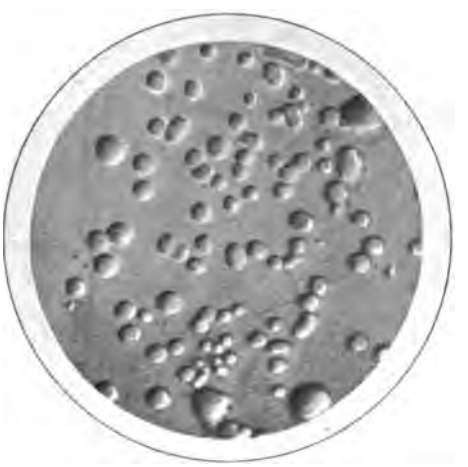
tained on animals. Two mice were inoculated with 1 c.c. each of the original growth in broth, one subcutaneously and the other intra-peritoneally. Two rabbits were inoculated with 4 c.c. of the original broth culture, one intra-peritoneally, the other intravenously. All four animals were alive and well a month later.

*Second culture, June 7th.*—The blood was spread over the surface of four large agar-plates. Only one colony appeared on the third day. This colony yielded a small bacillus in all respects similar to that previously obtained. This method of culture was evidently ill adapted to the growth of the organisn.

FIG. 12.

*B. influenzæ* in blood-culture. Fourth culture in Case 1. Colonies on agar-slope; fourth day.

FIG. 13.



*B. influenzæ.* Subculture, four days old, from one of the single colonies shown in the preceding fig. Typical dew-drop colonies. × 20.

*Third culture, June 20th.*—In twenty-four hours minute white colonies appeared in three broth-tubes; no growth was obtained on agar-slopes nor on three agar-plates. The colonies in broth grew rapidly, and on examination yielded a bacillus with characters as before described. The rabbit previously inoculated intravenously was again given by the same channel the greater part of a broth-tube containing a large number of the original colonies three days old. The animal was alive and well two months afterwards (August 27th).

*Fourth culture, July 2nd.*—Copious growth occurred in four broth-tubes and in the blood and condensation fluid of two sloped agar-tubes. Similar growth was obtained on two glycerine-agar tubes, but none on a solid serum tube, nor in milk. Glucose broth, however, showed good growth on the third day. One c.c. of the patient's blood was injected directly into the peritoneum of a guinea-pig, but without leading to any pathogenic effect. No growth was obtained in anaerobic cultures. The number of colonies which developed in the broth at this, the fourth culture, was very great. It was calculated that they exceeded one hundred per c.c. of blood.

An attempt was made to imitate the patient's disease in two rabbits. These were first inoculated intravenously with dead cultures of *B. coli communis*. Large quantities of the original blood-broth cultures were then injected into the animals' veins, one rabbit receiving the whole of a 10 c.c. broth-tube, containing an enormous number of colonies of the organism. Neither of these animals, however, developed any symptoms of disease; they were both alive and well three months after the experiment. On their being killed the heart of each was found to be quite natural.

The patient developed left hemiplegia a month after his admission to the hospital and right hemiplegia a month later. He died the next day, two months after he had come under observation and six weeks after the first blood-culture.

*Post-mortem examination.*—This was made thirty hours after death. A few petechiæ were seen about the neck and shoulders.

*The brain* showed some flattening of the convolutions of the right hemisphere. On section there was considerable softening of the cortex and centrum ovale on the right side, the colour being paler than natural. The right middle cerebral artery was

found to be plugged by an embolus which had lodged at the first point of branching of the vessel. There was no evidence of organisation of the clot. On teasing up a small portion of the embolus, non-Gram-staining organisms were demonstrable.

*The lungs* were engorged and œdematous. There were no infarcts and no areas of consolidation. There were old pleural adhesions on the left side.

*The intestines* contained two or three hæmorrhages.

*The spleen* weighed 10 oz., was large and firm, but contained no infarcts. Sections showed congestion only.

*The kidneys* weighed 12 oz. together; the surface and the cortex were mottled and pale. There were no infarcts. Sections examined by the microscope showed no special changes.

*The heart* weighed 23 oz. It was very large, the left ventricle being considerably hypertrophied; its wall measured 30 mm. in thickness. The interventricular septum was also very thick, measuring 28 mm. The aorta was stout and large, its diameter just above the sinuses of Valsalva measuring 45 mm. These changes in the organ were obviously due to old-standing incompetence of the aortic orifice, which was formed by two valves only, lying anteriorly and posteriorly, both much thickened and of unusual size; they measured 45 mm. in length at their free edge. There was no recent aortic endocarditis. The *mitral cusps* were thickened, but were also free from recent endocarditis. At a point on the wall of the left auricle just above the base of the anterior mitral cusp was situated a single mass of newly formed tissue, slightly pedunculated, firmly attached to the endocardium, dark red in colour, smooth and rounded in outline. It measured about 12 mm. in diameter. On examining the anterior of the two aortic flaps, it was seen that the mass of new tissue had penetrated the substance of the auricular wall and had produced a patch of small granulations which appeared at the base of this aortic cusp, some distance from its free margin.

*Bacteriological examination.*—The *heart's blood* proved to be sterile on agar, glycerine-agar, and in broth. This was probably due to the fact that thirty hours had elapsed between the patient's death and the *post-mortem* examination. Rubbings from the vegetations on the aortic cusp showed large numbers of small non-Gram-staining bacilli, morphologically resembling the influenza bacillus. No Gram-staining organisms were present.

Cultures from the vegetations on blood-agar plates showed typical colonies of *B. influenzæ* with a few contaminations (yeasts). Cultures from the spleen were sterile on blood-agar and in blood-broth.

CASE 2.—Frederick T—, aged 13 years, was admitted to the Great Northern Central Hospital on November 8th, 1904, suffering from mitral disease and irregular fever.

*Blood-culture.*—Undertaken on two occasions. Technique as in Case 1.

*First culture, January 2nd,* 1905.—Growth appeared on the second day, in four broth-tubes and on two agar-tubes, the colonies quickly becoming large and opaque in the broth-tubes. They were very numerous. On the agar-slopes the colonies were also very numerous, close to the condensation fluid, running together into a semi-translucent layer of growth; the condensation fluid itself was crowded with colonies. A few colonies appeared upon the general surface of the sloped medium. The organism resembled that obtained in the previous case in every respect. The growth was pure.

*Second culture, January 28th.*—Again there was a very copious growth in all six tubes, the colonies being even more numerous, at least 100 per c.c. of blood. The growth was again pure.

Six weeks after admission to the hospital signs of kidney disease appeared, scanty urine, containing much albumen and casts, and œdema. The patient died three weeks later, nine weeks after he had come under observation, and five weeks after the first blood-culture.

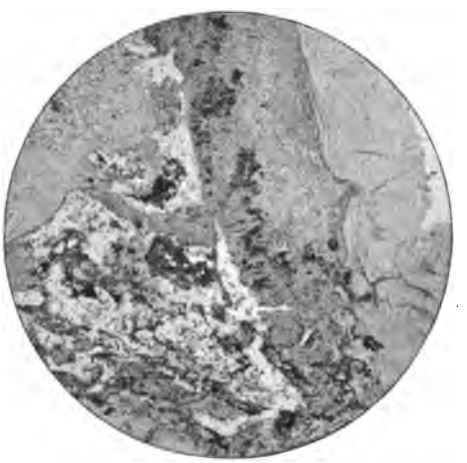
*Post-mortem examination.*—This was made twelve hours after death. The only organs presenting any pathological change were the heart, spleen, and kidneys.

*The heart* weighed 8½ ounces. Both sides were somewhat dilated and the left side was hypertrophied. The myocardium was pale and showed granular degeneration under the microscope. The mitral valve was thickened and somewhat stenosed, these changes being evidently of some considerable duration. Sprouting from the posterior aspect of the fused mitral cusps was a single mass of rounded "vegetation," obstructing the orifice in such a way as to readily suggest that this was the

cause of the musical systolic murmur which had been a clinical feature of the case. The whole mass was about 10 mm. in diameter; its surface was smooth. There was no destruction of tissue, neither of the valve nor of any other part of the heart.

*The heart's blood* was sterile on cultivation. A piece of *the vegetation* rubbed over the surface of two glycerine-agar plates yielded, besides air contaminations, numerous colonies of *B. influenzæ,* which were subcultivated on blood-agar. Films made direct from the vegetation yielded large numbers of minute non-Gram-staining bacilli, having all the characters of *B. influenzæ.* No Gram-staining organisms were found in the films.

FIG. 14.



**Influenzal endocarditis. Section through mitral valve in Case 2, showing deep invasion of the tissue by the bacillus. × 45.**

A section taken through the *endocardium* at the site of the vegetation showed a layer of fibrin beneath which lay dense masses of organisms. Deeper than these masses, in the loose endocardial connective tissue, there were seen other groups of organisms, less crowded together and therefore more easily studied. They were short bacilli, often seen to be diplo-bacillary in form, and here and there some of the thread-like bacilli already described were plainly seen. The depth to which the organism had penetrated the tissue was very striking. None of the organisms present took Gram's stain.

*The spleen* weighed 5 oz.; there was extensive old perisplenitis

and three or four old infarcts, white and sunken, the largest of which occupied about a quarter of the whole organ. Cultivations from the splenic pulp yielded no growth of any organism, nor did sections of the spleen show any on microscopic examination.

*The kidneys* weighed 12 oz. They were large and pale, the surface mottled, the cortex swollen and very pale. Several old infarcts were present. The microscope showed very little change in the general kidney substance. There was some recent infiltration of the cortical interstitial tissue. The cells of the convoluted tubules showed some granular degeneration.

There seems no doubt that in the two instances here dealt with a condition of influenza septicæmia was present. They therefore form a striking contrast to the ordinary cases of influenza, in which, despite the earlier assertions of Canon, it is now agreed that the bacillus does not invade the general blood-stream. The focus of the disease was in both cases the endocardium. Henceforth to the already rich flora of endocarditis must be added Pfeiffer's influenza bacillus. So far as can be concluded from these two cases there would seem to be little tendency to destructive changes in the heart, but rather to the formation of new masses of material of considerable size, firm and rounded. In the heart first described the situation of the mass suggests direct infection of the auricular wall by organisms arriving in the pulmonary blood-stream. The presence of a congenital defect—two aortic cusps—incidentally illustrates the special tendency this gives to infective endocarditis.

In the above account clinical details have been purposely excluded. They will appear elsewhere. It may be stated, however, that the illness in both cases appeared rather insidiously; there was no initial disease which bore any obvious resemblance to the ordinary forms of influenza. Both cases ran a prolonged course; one probably lasted three months and the other one four months. In both instances the influenzal infection was grafted upon an endocardium which had been damaged by previous attacks of rheumatism. A point of some pathological interest is the fact that in each case a well-marked leucocytosis was present. In the adult case the highest count was 18,400; in the case of the boy the highest count was 22,400. So that whatever may obtain in ordinary attacks of influenza—and it seems certain that these usually give no leucocytosis—it would seem that influenzal

*septicæmia* leads to considerable increase in the number of leucocytes.

As to the frequency of the disease, future observations can alone show whether the discovery of these two cases within six months of each other constitutes a mere coincidence, or whether, as is more likely, the condition is in reality not very uncommon. It not infrequently happens that in cases of "malignant" endocarditis, cultures made *post mortem* fail to reveal the nature of the organism in the heart-valves. And often no investigation of this kind is made. It may be that some of these cases are really influenzal in character. I also think it not unlikely that some of the cases thought to be streptococcal may be influenzal. Coverslip preparations made from the vegetations in these two cases gave a strong superficial resemblance to a short streptococcus. To employ Gram staining in every instance is the safeguard against such an error in diagnosis.

*April 18th*, 1905.

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## 6. *An example of true hermaphroditism in the domestic fowl, with remarks on the phenomenon of allopterotism.*[1]

By S. G. Shattock and C. G. Seligmann.

(With Plate I.)

## *De hermaphroditismi exemplo veri in* Gallus bankiva.

(Cum tabulâ I.)

Summarium.

Haec avis (in museo collegii regii chirurgorum Anglici nunc conservata) annorum duorum ætatis et varietatis Leghorn, ut appellatur, cristam monstrat masculinam atque calcares, femineam autem caudam.

Nunquam sexualiter functa est.

[1] This name we venture, for convenience, to give to the transformation of plumage in birds, whether of the female to male or *vice versâ* (ἄλλος, other; πτέρωτος, feathered.)

Dissectio oviductum sinistrum ad normam evolutum demonstrat, oviductum dextrum brevem atque tenuem.

Vas deferens utrumque adest, et latere utroque glandula generativa cujus superficies minute convoluta. Glandula generativa sinistra ex tubulis testicularibus constat, quorum nulli funguntur. Partis inferioris in sectionibus microscopicis ova duo in glandulâ apparent, quorum utrumque pariete folliculari circumtegitur.

Ovi utriusque in vitello adest vacuolum eccentricum ovale, quod in unâ e sectionibus rete chromatini includit. His sectionibus seriatim factis probantur ova esse spherica; tubuli distenti ergo excludi possunt.

Glandula generativa dextra aliquantum minor quam sinistra, e tubulis quiescentibus similiter constat; singulo in loco autem inveniuntur tubuli cellulis distenti in quibus spermatogenesis progreditur.

Quum glandula utraque vase deferenti prædita est, avis sicut et mas et femina se gerere forsan potuisset.

Ex his opinari inducti sumus illam pennarum mutationem apud aves in quâ femina notas maris externas proponit, conditionem bisexualem glandularum generativarum indicare.

Hæc mutatio in speciebus avium plurimis invenita est, sed in *Phasianus Colchicus* frequentissime et in *Thaumalea picta*.

Nobis sunt insuper exempla in *Anas boscas*.

In casibus quibusdam mutatione aliquatenus progressâ avis notas rursum acquirit femineas.

Avis masculina notas externas raro proponit femineas.

In uno exemplo quod indagamus, pennæ singulæ crescentes caudæ mutabantur, parte remotâ pennarum singularium notas monstrante maris, parte alterâ illas feminæ (vide tabulam I).

Avis eadem, pennis positis, notas nullas femineas adhuc monstrabat.

Pennis mutatis sexus appetitus simul mutatur; avis sicut mas se gerit.

In illis avibus quæ notas maris externas acquirunt, dissectio ovarium tabescisse probat.

Ovarii atrophiam, tamen, haud opinamur hæc phenomena explicare, quæ causari putamus actione telæ glandularis masculinæ aut cum ovario admixtæ aut alibi collocatæ.

Aves illas, quidem, hermaphroditos esse credimus.

The ultimate criterion of sex resolves itself into the structure of the reproductive glands. An abnormal disposition of the sexual passages or misdevelopment of the external generative organs may lead, it is true, to ambiguity of sex during life, but such aberrations do not constitute the condition of true hermaphroditism.

In its full and strict sense true hermaphroditism supposes, not only a bisexual structure of the reproductive glands, but the capacity in a single individual of performing both male and female functions and of producing, simultaneously or at different times, a fertilising sperm and fertilisable ova.

The bird with which the present communication deals is a two-year-old Leghorn fowl, which possesses, in addition to male and female sexual ducts, a gland on the right side which appears to be only male, whilst a larger gland on the left is composite, or bisexual.

The fowl was received alive from the office of the 'Field' newspaper, through the kindness of Mr. W. B. Tegetmeier, to whom it was sent on account of its obvious peculiarities.

Externally it presents certain features characterising the adult of each sex. It exhibits the fully-developed comb and wattles of the cock, which are of a brilliant red colour; the comb, however, droops slightly to one side as it does normally, though not to the same extent, in the hen, the comb of which, in the Leghorn variety, is of conspicuous size.

Each leg bears a thick, blunt spur, nearly an inch in length.

Amongst Leghorn fowls it should be noted that the occurrence of spurs is by no means uncommon in hens of a certain age and which have not necessarily ceased to lay. In plumage the characters are mainly female. The neck hackles are but moderately developed; the saddle hackles practically absent; the tail, though not typically feminine, is quite destitute of the curved, sickle feathers present in the cock.

Regarding its sexual physiology, the bird had never laid or shown any sexual proclivities, either male or female, nor did its

FIG. 15.

The leghorn fowl described in the text. It presents the fully-developed comb and wattles, with the spurs, of the cock, but the tail is quite devoid of curved or sickle feathers, and resembles that of the hen. From a photograph taken during life.

EXPLICATIO FIGURÆ.

Avis, hermaphroditus, annorum duorum (Gallus Bankiva). Cristam monstrat masculinum atque calcares, femineam autem caudam.

presence excite any notice from other birds of either sex with which it was kept. It was not heard to crow, but would at times give a throaty screech.

**Dissection** of the trunk reveals the presence of two oviducts.[1] That of the left side is fully developed and has a normal dis-

[1] This specimen, together with the skin of the bird set up from a photograph taken during life, is now in the museum of the Royal College of Surgeons, Teratological Series, Nos. 711 A, 711 B.

FIG. 16.

A dissection of the viscera of the hermaphrodite fowl described. Beneath the vas deferens of the right side as it courses over the lower part of the kidney, to the inner side of the ureter, a fine rod of white glass has been passed. A loop of black bristle has been placed in the upper end of the left oviduct. The left reproductive gland lies at the highest part of the specimen; it is a flattened body about 3 cm. in length, and has a convoluted surface. The highest body on the right side, transfixed with a rod of white glass, is the right adrenal; the left adrenal is hidden by the summit of the left reproductive gland. The smaller reproductive gland of the right side lies nearly opposite the middle of the left.

EXPLICATIO FIGURÆ.

Monstrantur dissectione; oviductus sinister ad normam evolutus; vas deferens dextrum super partem renis inferiorem; glandula generativa sinistra cujus superficies minute convoluta; et glandula generativa dextra aliquantum minor quam sinistra. Corpus suprarenale dextrum cum setâ albâ infigitur; corpus sinistrum latet.

position, its upper end being widely patent; the right is diminutive and of less than half the full length, its upper end lying near the lower border of the right kidney. There is a pair of sexual glands separated by a median fold of peritoneum. The gland of the *left* side is of flattened form, about 3 cm. in chief, vertical, diameter, of pale yellow colour, and presents a convoluted surface like that of the cerebrum in miniature.

The sexual gland of the *right* side is considerably smaller (about a fourth of the left), but presents similar macroscopic characters.

On each side there is a vas deferens; on the left the duct has been traced from the sexual gland for its whole length; on the right, the upper end has been cut away. A microscopic examination of a portion of the right duct revealed the normal convoluted structure. The natural orifices of the oviducts and vasa deferentia were taken away in the removal of the skin from which the bird was afterwards set up: the lower end of the left oviduct where cut across is fully pervious.

The adrenals are normal and occupy the usual position.

**Histology.**—The larger gland of the *left* side has a typically tubular structure. The tubuli are bounded by a thin, normal, basement membrane, and the tubular epithelium is constituted by a single layer of elongated cells, the nuclei of which lie basally, near the membrane named. The cells which line the tubuli are prolonged centralwards; so that, notwithstanding the fact that nearly every tubule is of conspicuous diameter, it has no proper lumen, but is filled with a somewhat coarsely vacuolated substance, produced, in part at least, by the inner portions of the cells, which have become broken up, and look, as it were, frayed out in the central part of the tube. That the cells are not dead is proved by the fact that their nuclei fully take the hæmatoxylin stain, and present a normal character. None of the tubuli in the portion of the gland examined show any signs of activity; no mitosis or cell-proliferation is in progress. The tubules vary somewhat in diameter. The smallest are disposed more particularly near the free surface of the convolutions of the gland, but the transitions of size may be readily traced, in favourable longitudinal views, even in the same tubule. The free surface of the gland is covered with columnar, *i. e.* germinal, epithelium, but no continuity of the tubular epithelium with this was encountered in the sections prepared. The columnar epi-

thelium lining the lesser tubuli is more regularly disposed and smaller than in the larger.

The stroma between the larger tubuli is scanty, but conspicuous groups of polyhedral interstitial cells occur in it.

At the surface of the gland the stroma is more abundant, and supports the smaller tubuli already referred to: it is here, as elsewhere, highly cellular, and contains in addition groups of polyhedral interstitial cells similar to those in the deeper parts.

FIG. 17.

A microscopic section of the left reproductive gland, showing tubuli of various sizes; of the smallest, a group of three, in transverse section, lies near the free surface. None of the tubules are functionating. ($\frac{2}{3}$ objective.)

EXPLICATIO FIGURÆ.

Sectio microscopica glandulæ generativæ sinistræ. Monstrantur tubuli glandulares magnitudinis diversæ, quorum nulli funguntur.

Beyond this, though intimately continuous with it, there succeeds the less cellular investment of peritoneum bounding the gland.

There is no fibrous tunic comparable to the tunica albuginea, although the gland is testicular in its histological character: in its external configuration, in fact, it resembles an ovary in the quiescent phase, except that its degree of lobulation or convolution is grossly exaggerated.

In the serial sections made of the lower end of this, the left, gland two ova were found. The general structure of this portion of the gland is precisely like that of the rest as already detailed. The larger of the two ova lies in one of the convolutions of the gland and projects slightly from it, being covered on the superficial aspect by a thin layer of stroma. It comprises peripherally a single layer of cubical or subcolumnar cells, *i. e.* a follicular wall, and within this a finely granular-looking content presenting an excentric oval space of conspicuous size. The neighbouring tubuli of the convolution are compressed by the structure in question, the spherical figure of which is made clear by the mode of its disappearance in the serial sections; for after somewhat rapidly diminishing in size, the vitellus vanishes, a circular mosaic of cells representing the follicular wall is brought into view, and in the next succeeding section this has likewise vanished.

In the reverse direction the body is similarly traceable almost to its source, though the latter itself is just missed in the end of the ribbon.

The circumference of the vitellus is not in all the sections regular, but may be dentate from shrinkage; in ova of corresponding size in the normal ovary a similar appearance is to be met with. The substance of the vitellus presents a certain number of vacuoles, each of which contains a somewhat deeply-stained granule. In the serial sections the space representing the nucleus or germinal vesicle, after diminishing in size, suddenly disappears, its spherical form being in this way established. In some of the sections a lacuna is all that represents the germinal vesicle, but in others the void is filled with a finely granular material in which there ramifies a widely-open net taking the hæmatoxylin stain.

In addition to this ovum a second was encountered. That the two bodies are quite distinct appears from the fact that after the disappearance of that already described an entire slide of three tiers of ribbons intervenes, in which the only structures present are inactive testicular tubuli.

In the slide next succeeding, the second ovum occurs, and in this slide both the origin and the disappearance of the latter can be readily traced. The ovum is slightly smaller than the other and less oval in form. It lies at the free surface of the gland

near the peritoneal reflection, and on one aspect is contiguous with inactive testicular tubuli. The follicular wall consists of a single series of cubical epithelial cells.

The body first manifests itself in the sudden appearance of a disc or circular mosaic of epithelium; in the section succeeding, the disc is replaced by an epithelial ring enclosing a central vitellus; the structure increases in size, a conspicuous space answering to a germinal vesicle appears in the vitellus, and the body as a whole, after reaching its maximum, diminishes, the vacuole disappears, and the last remnant presents itself, exactly as did the first appearance, in the form of a simple circular, epithelial mosaic. The space in the vitellus which represents

FIG. 18.

A microscopic section of the lower end of the left reproductive gland. Lying in the stroma, at the free surface, there is an ovum with vitellus and germinal vesicle, enclosed within a follicular wall. (⅛ objective.)

EXPLICATIO FIGURÆ.

Sectio microscopica glandulæ generativæ sinistræ. Monstratur ovum pariete folliculari præditum.

the site of the germinal vesicle appears and vanishes in a succession of four of the serial sections.

In the serial sections of the higher portion of the same, left, and larger gland no ova were encountered amidst the inactive tubuli.

In addition to this evidence of the nature of the two bodies in question it is to be remarked that there are nowhere any tubuli distended by retention. And besides this, they can be exactly matched in sections of the ovaries of normal birds. In

certain of the ova in the normal ovary, the site of the germinal vesicle is represented by an excentric space, the size of which relatively to the vitellus precisely corresponds with that in the ova of the hermaphrodite gland, the emptiness of the vesicle in either case being, of course, an artificial result occurring during the preparation of the section. The cells of the normal follicle are similarly constituted by a single series of cubical form. The stroma of the normal ovary is highly cellular, and in the chick, even at the seventh day after hatching, it contains conspicuous groups of finely vacuolated interstitial cells.

FIG. 19.

A microscopic section of the right reproductive gland. Some of the tubuli are of conspicuous size and distended with actively dividing cells ($\frac{2}{3}$ objective.)

EXPLICATIO FIGURÆ.

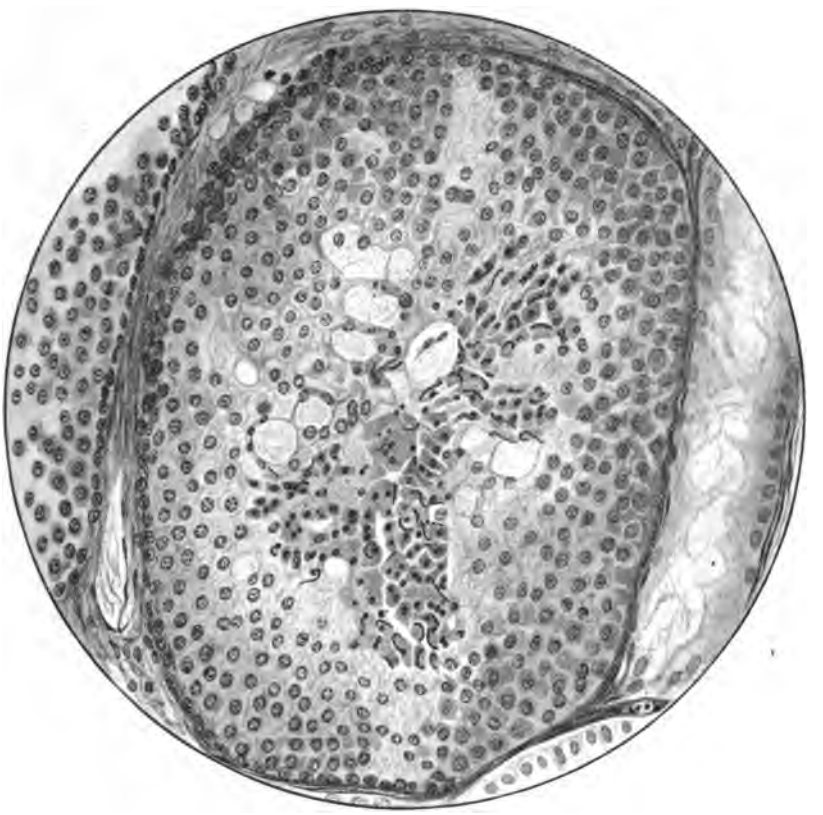
Sectio microscopica glandulæ generativæ dextræ. Tubuli quidam magnitudinis insignis, atque cellulis distenti sunt.

In regard to the gland of the *right* side nothing suggestive of an ovum was met with in the portion cut into serial sections. Its structure exactly repeats that already detailed, with one important exception. Lying amidst the general collection of inactive tubuli in one of the convolutions of the gland, there is a microscopic area in which the tubules are of conspicuously greater diameter than elsewhere, and distended with closely

packed epithelial cells the nuclei of many of which present mitotic figures. In the more central cells of one of these active tubuli spermatogenesis is in progress.

It may be noted in regard to this particular tubule that for about half its circumference it lies in juxtaposition with tubuli

FIG. 20.



The lowest and largest tubule of the preceding figure, more highly magnified. The tubule is full of actively dividing cells; in the centre spermatogenesis is in progress. ($\frac{1}{8}$ objective).

EXPLICATIO FIGURÆ.

Tubulus in sectione præcedenti infimus et maximus. Distenditur cum epithelii cellulis; in medio tubulo progreditur spermatogenesis.

which exhibit no marks of activity and are not more than a third of its diameter. The transitions between the active and inactive phases are readily traceable.

To complete the histological side of the specimen, the nature of the smaller tubuli in the left gland demands consideration, as likewise does the meaning of the large size of the general tubuli in spite of their physiological inactivity. That the smaller tubuli which lie at the free surface of the gland are testicular appears from the circumstance that they can be distinctly traced into the larger, and do not occupy the position of the epididymis.

Their diminutive size may be explained by viewing them as immature or hypoplastic, for the reason that in the testicle of the young bird the tubuli present a precisely similar picture.

In the chick of the common fowl, on the seventh day after hatching, microscopic transverse sections of the entire testis (2 mm. in chief horizontal diameter) show an abundant stroma, in which there lie groups of polyhedral interstitial cells.

The tubuli, which are much convoluted, and some of them distinctly branched, present a simple lining of elongated cells with basal nuclei. With scarcely any exception, they are devoid of lumen, and none exhibit any differentiated centre. The tubuli are fairly uniform in diameter, though narrow isthmuses occur where the section has failed to strike the centre of a loop.

A comparison of the tubuli with the smaller of those in the gland of the hermaphrodite fowl demonstrates a complete correspondence in size, in the character of the cell-lining, and absence of lumen. The presence of smaller tubuli in the immediate neighbourhood of the tunica albuginea is to be encountered, moreover, in the normal testicle of the young adult bird, as we have seen in the pheasant.

The conspicuous size of the tubuli in general does not allow of a satisfactory explanation. The coarsely vacuolated lumen which they present suggests the possibility of a secondary series of cells having at some time occupied its meshes. And seeing that both the glands are provided with a proper vas deferens, such cells or their *débris* may have at some time passed onwards out of sight. If this were so, however, it would by no means necessarily imply that spermatogenesis had been reached; indeed, it is impossible to think that the bird would have failed to present the full male characters had spermatogenesis occurred in such a bulk of tissue. It may be noted, moreover, that the

tubuli, although large, are markedly smaller than those of the right gland, in which spermatogenesis is actually in progress.

A study of the right gland leads no farther. In the central mesh of the functionless tubes, around those in which spermatozoa are developing, a certain number of smaller cells are to be met with, but the fact that such occur without spermatozoa only indicates that the tubuli of the opposite gland may have held similar cells and yet no spermatozoa.

### Remarks.

This bird must be classed as a true hermaphrodite, since its reproductive glands are bisexual; there is an ovotestis on the left side and apparently a testis alone on the right. Not only is it bisexual in this, the essential criterion of sex, but being possessed of both sets of generative passages, the bird was potentially capable of performing both male and female functions. It is of interest to observe that on the left side, on which the oviduct is fully developed, the reproductive gland contains the ova described, and that the testicular tubuli are inactive, whereas on the right side, on which the oviduct, though abnormally present, is diminutive, the reproductive gland (in that portion, at least, submitted to examination) presents no ova, but a group of active testicular tubuli.

## Transformation of Plumage in Birds: Alloptèrotism.[1]

### (1) Of the Female Plumage into that of the Male.

The bisexual external characters displayed by this bird, associated as they are with a bisexual structure of the reproductive glands, have led us to frame an hypothesis with respect to a long and well known phenomenon, viz. the assumption in birds of the plumage of the opposite sex. This phenomenon, to which we venture, for convenience, to give the name of "allopterotism," usually shows itself as a transformation of the characters of the female into those of the male; cases of the converse kind, in which the male acquires female characters, are particularly rare, if we except those occurring in certain hen-feathered breeds of the domestic fowl. The change more commonly affects the older

[1] ἄλλος, other; πτερωτος, feathered.

hens, which cease to lay and thereupon assume certain or all of the external characters of the cock bird. It is to be observed, however, that well-marked examples of the same change occur in young birds after the first moult; this we have on several occasions witnessed in the common pheasant (*Phasianus colchicus*).

Yarrell[1] states that amongst pheasants reared by hand some females at the age of only four months may produce the brightest plumage of the male, and that in two instances the same appearance was encountered in birds shot in a wild state, the nest feathers not having been shed, a proof that the birds were of the year.

Although best known in the common pheasant, it has not infrequently been observed in the golden pheasant (*Thaumalea picta*), more particularly in the case of older hens; yet we know of one instance in which the full male plumage was assumed after the first moult. In this particular case no spurs had appeared; the bird when killed was three years old, and had not laid or shown any sexual instincts.

In the Japanese pheasant (*Phasianus versicolor*) there is an example of the transformation, in the Royal College of Surgeons (Physiological Series, v. 27). The bird was more than twelve years old and had ceased to lay; the plumage assumed is that of the cock, but no spurs have grown. Yarrell (*loc. cit.*) states definitely that the legs and feet retain the smaller and more slender female characters and are without spurs.

We have been enabled, however, through the kindness of Mr. W. E. Downing, to examine a prepared bird in which short spurs have grown. The assumption of male plumage in this case, notwithstanding, is but very little advanced, and hardly amounts to more than some darkening and faint iridescence of the feathers at the base of the nape; the tail is not abnormally long,[2] and presents the usual female marking; each leg bears a sharply pointed spur 7 mm. in length. The bird was shot.

The phenomenon, however, is by no means confined to any particular species of bird. It has been recorded, amongst

[1] 'Phil. Trans.,' 1827, p. 268, "On the Change in Plumage of some Hen Pheasants."

[2] It may be here observed that in some cases the earliest evidence of alloptorotic change in the hen pheasant is an increased length of tail, which, in this feature, comes to resemble that of the cock, although it may not exhibit the male markings.

## EXPLANATION OF PLATE I,

Illustrating the paper by Mr. S. G. Shattock and Mr. C. G. Seligmann on "A Case of True Hermaphroditism in the Domestic Fowl," etc. (P. 69.)

One of the tail feathers of a common cock pheasant (*Phasianus colchicus*) in which a partial transformation of plumage to the female type occurred. The distal end presents the typical markings of the cock, the proximal those of the hen. (Natural size.)

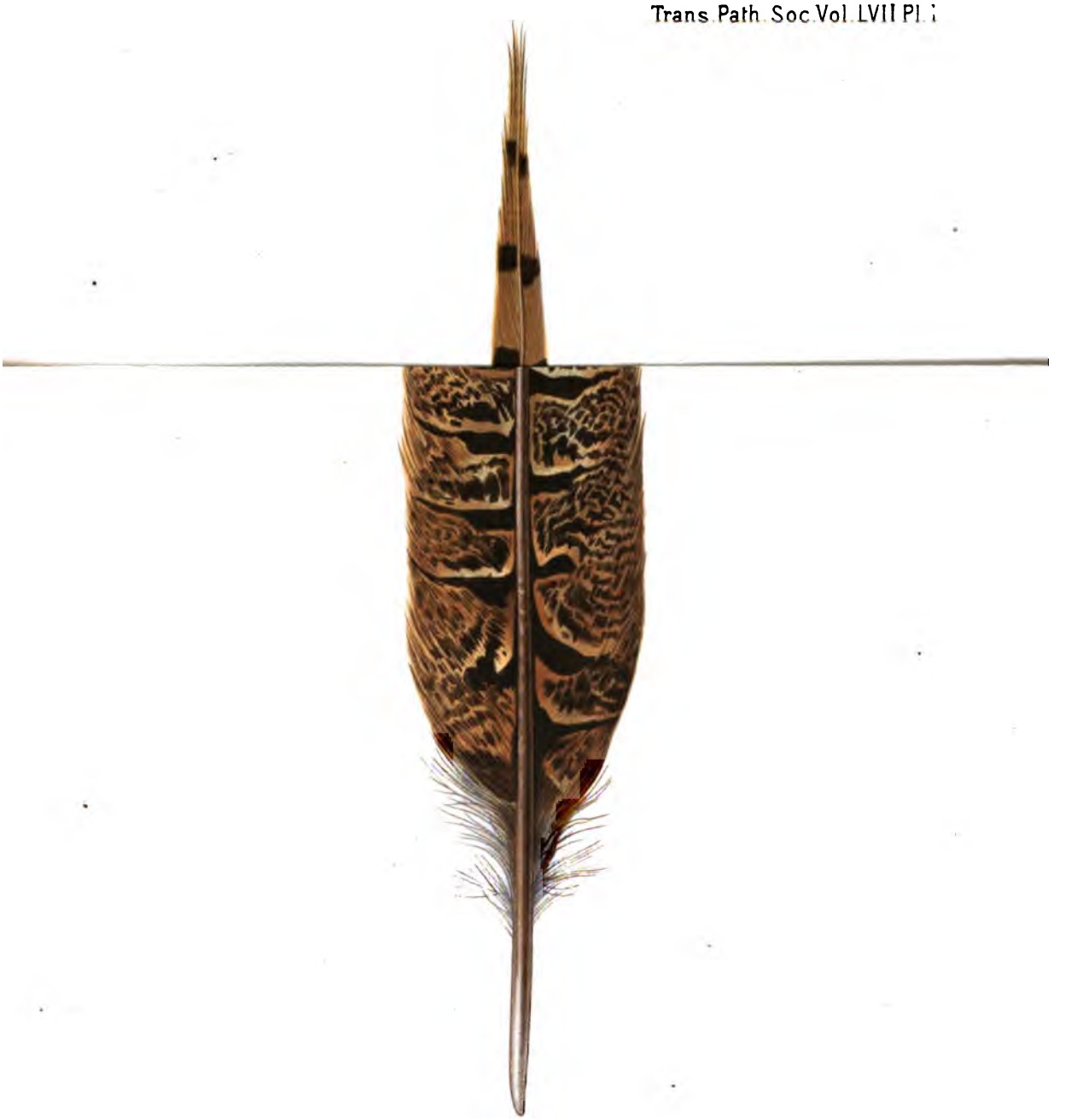
The specimen is now in the Museum of the Royal College of Surgeons, London.

## TABULA I,

S. G. Shattock and C. G. Seligmann. (P. 69.)

**Ad dissertationem "De hermaphroditismi exemplo veri in *Gallus bankiva*" illustrandam.**

Una e caudæ pennis phasiani masculini (*Phasianus colchicus*).
Extremitas remota notis signatur masculinis; altera, notis femineis.
Hæc avis, pennis positis, notas nullas femineas adhuc monstrabat.



Lith. Anst. v. E. A. Funke, Leipzig

others, in the peahen, turkey, partridge, black cock, pigeon, kingfisher, bustard, American pelican, domestic duck, wild duck, and often in the domestic fowl.

In the Museum of the Royal College of Surgeons there is the train of a peahen (Physiological Series, v. 26) which is identical with that of the male. The bird was believed to have been more than thirty years old, and for some years had ceased to lay; the assumption of male characters was gradual. The

FIG. 21.

The tail of an Aylesbury duck. The bird, after ceasing to lay, acquired the up-curled feathers in the tail which characterise the plumage of the drake. (Nat. size.)

EXPLICATIO FIGURÆ.

Anatis cauda domesticæ, varietatis Aylesbury, ut appellatur. Avis parere destiterat, et pennas caudæ inflexas quæ maris propriæ sunt postea acquisivit.

blue on the throat was greener than in the cock, and the dark markings on the wing coverts larger and less clearly defined.

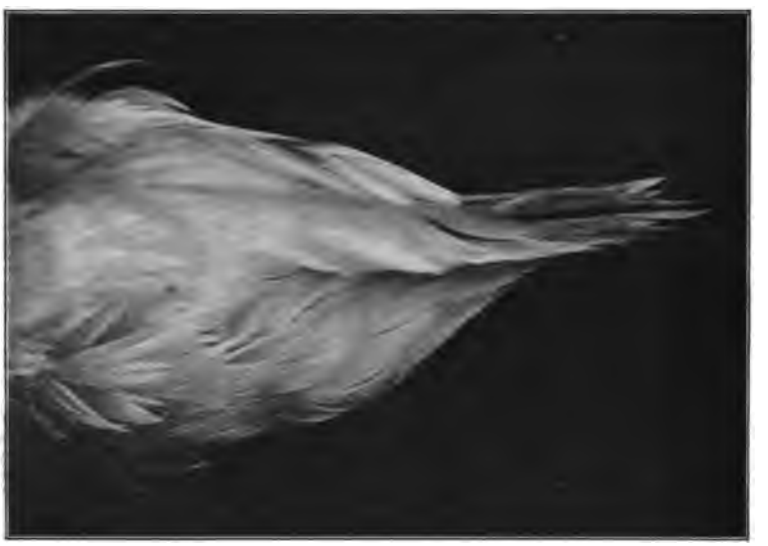
In the domestic duck (Aylesbury strain) we have seen one instance. The bird, which we received alive, through the kindness of Mr. W. B. Tegetmeier, was of particularly large

size, and pure white in plumage. After ceasing to lay it acquired the up-curled feathers of the tail which characterise the drake.

The most pronounced examples, however, in the duck which have fallen under our observation have been in the wild bird (*Anas boscas*), in which the vivid colours of the mallard make the transformation particularly striking.

In February, 1903, we received, through the kindness of

FIG. 22.



'The tail of a normal Aylesbury duck, showing the absence of the up-curled feathers which characterise the plumage of the male.

EXPLICATIO FIGURÆ.

Anatis maris cauda, varietatis Aylesbury ut appellatur.
Pennarum nullæ inflexæ sunt.

Mr. W. B. Tegetmeier, from Mr. Leno, of Hemel Hempstead, two wild ducks which had assumed male plumage. One of these we killed for examination in July, 1903; the other is still alive in the gardens of the Zoological Society. The detailed condition of this bird on October 6th, 1905, in which month the normal drake has assumed its full winter plumage, was as follows: Bill—distal fourth of upper beak dull pink in

colour; the rest of a deep black, with the exception of an orange margin, which is spotted with black; the "nail" or "tooth" black. In the typical mallard the bill is of a uniform pale olive-green, and is likewise furnished with a black "tooth." Vertex and upper part of nape glossy green; sides of face brownish, speckled with glossy-green feathers; hyoid region brownish, with a patch of glossy green; lower part of nape of a greyish-brown, passing into the greyish feathers of the interscapular region. The white ring (normally present in the mallard) is indicated in front and at the sides by a few whitish or partly white feathers. Below these the feathers of the breast are of a dark chestnut, sometimes irregularly blotched with black, and where the breast joins the belly edged with white; the colour of the breast is less vivid and dark than in the normal male. Belly of a greyish brown, many of the individual feathers wholly or partially faintly vermiculated. Flanks generally of a brownish colour; they present a number of partially, and few fully, vermiculated feathers. Interscapular feathers dark, more or less faintly vermiculated; below these the feathers of the back are dark and towards the tail assume a green, metallic gloss. Wing coverts and wings typically male, the primary wing feathers of a cold or blackish brown; the secondaries show a metallic zone of intense blue or violet, tipped with black and white.

Of the classical instance of allopterotic change in the domestic fowl, "the crowing hen," we are unable from our own observation to describe a typical example. It would seem that the hen after ceasing to lay assumes to a greater or less extent the male plumage and takes to crowing.

In one case, a hen now set up and in the collection of Mr. W. E. Downing, the comb has retained the female character, but long sharp spurs have developed on the legs, the neck hackles are fully male, and the tail contains a good show of long sickle feathers. This bird came from the collection of Sir William Jardine; the record of its sexual history is not preserved.

In another case, observed by Mr. Frank Finn, a gold-pencilled Hamburg hen which had laid, grew spurs and was heard to crow without acquiring male plumage.

**Barrenness in Allopterotic Birds.**

That birds the plumage of which undergoes a transformation from the female to the typically male kind as a rule first become barren has been our experience, and in this our observations accord with those of others.

The sterility accompanying the transformation is doubtless the innuendo underlying the rhyme—

> "A whistling maid and a crowing hen
> Are good to neither God nor men,"

variants of which couplet are to be found in many languages.

That this is not invariably so, however, is shown by Homeier's case, to be presently again referred to, in which a hen became cock-feathered at the second moult, but continued to lay eggs and to hatch chickens. We have ourselves observed the same in the case of one of the two wild ducks already referred to, which had assumed the plumage of the mallard.

During the summer of 1903 these two birds were kept in an enclosure with a normal mallard for the purpose of noticing whether they would pass through the seasonal change of plumage which normally occurs in the male during the summer. One of these mallard-like ducks laid two eggs, which were incubated beneath a hen for at least a week; at the end of this time the eggs were opened, when one was found to contain a small embryo. In this instance, then, the female, after having acquired the male plumage, retained the functions of its original sex. This is unusual. As a rule the transformation of the feminine to the masculine plumage is accompanied with a corresponding change in sexual physiology.

Amongst domestic fowls the hens which have acquired the comb and the external characters of the cock have been observed to "tread" other hens, and we may extend the observation by stating that the same is true, *mutatis mutandis*, of the wild duck.

**Occasional Transience of the Allopterotic Change.**

An occasional and noteworthy feature in the phenomenon of allopterotism is the transient character it sometimes presents when appearing late in the life of the bird, and this not only when the assumed marks of the opposite sex are merely partial or little developed, but even when they have become well pronounced. It seems as though a wave of maleness, comparable

with that of puberty, swept over the organism, which becomes during its passage profoundly modified. That the psychical change accompanying the transformation would be transient, the cutaneous change persistent, is what would *à priori* have been anticipated. Nevertheless, a temporary assumption of external characters is a well authenticated phenomenon.

The temporary nature of the psychical change we may illustrate by an observation made in the case of a third wild duck. This bird, a decoy, exhibited, it may be remarked, a considerable admixture of the common domesticated strain, as proved by its heavier build and greater size, yet it flew well. She had laid and hatched her brood regularly until five years ago. At this date laying ceased, and she commenced, it was stated, to put on the mallard's plumage. Her breast began to change in colour, and the neck showed a white ring which had not been previously there. The bird grew curly feathers in the tail, and her general appearance was that of a drake, for which it was generally taken until made to fly, when the voice, which remained throughout that of a duck, betrayed her true sex. During, and for a few months after this physical change, the bird courted and went through the action of treading another duck in captivity with her precisely as a mallard would have done, whilst she, moreover, avoided the attentions of a mallard to whom she remained alluring in spite of her change of plumage. As her wings were unclipped there was no difficulty about this.[1]

Through the courtesy of Major Turle, whom we take this opportunity of thanking, the bird came into our possession early in September, 1903. At this time she possessed the curly tail of the male, and her general appearance was that of a mallard. In this case, then, accompanying the assumption of male plumage there was an assumption of male instincts. The latter, however, were transient, and on their disappearance there followed, not a reassertion of the instincts of the female, but a psychically asexual condition.

Such a retention of external male characters after the disappearance of male instincts corresponds, in fact, with what

[1] We are aware that ducks in general are particularly indiscriminate in their sexual approaches; the regularity of psychical perversion, however, in allopterotic ducks constitutes a phenomenon not to be ignored in connection with the problems under consideration.

happens normally in old age, where the external marks of sex persist after the sexual functions have ceased.

A striking example of the transience of certain of the late assumed external sex characters in allopterotic birds is recorded by Homeier. A hen became cock-feathered at its second moult, but continued to lay eggs and to hatch chickens. At the third moult it again produced cock feathers, but at the fourth moult the bird re-assumed the hen's plumage.

Of the converse case, in which a male pheasant assumed in part the plumage of the hen, but for a season only, we give an instance later.

How far it is strictly and invariably true that no disappearance of any of the external male characters follows the termination of sexual function is a question upon which further observation is required. Here, possibly, a difference obtains in the case where the sexual functions cease naturally from age and in that where these functions are cut short by castration carried out upon the still functional adult.

In regard to the second class of case, we may record an observation made upon a Leghorn cock, which was castrated when about five months old by Professor A. Watson of Adelaide. The testicles when removed in November, 1903, were of the full size; the bird was killed in October, 1904—*i.e.* about a year after the operation. During that time the comb and wattles (which were well developed at the date of the operation, though the spurs were short) were observed by Professor Watson to slowly diminish in size. The bird would occasionally crow, but in a feminine style. The tail, presumably after the moult, took on the following characters: it contains two conspicuous sickle feathers which differ from those of the normal cock in their greater length and slenderness, as well as in the shallowness of their curve. The sickles, in short, are such as are found in cock birds which have been caponised before maturity. In addition on either side of the sickles there is an unusually long round-ended feather like those in the male but differing in its excessive length. The tail was pronounced by Mr. Frank Finn to be "overfurnished," as it is in the capon. No testicular remnants were discovered in the abdomen after the bird was killed.

It is a matter of considerable interest that at the date of castration, in November, 1903, the spurs were scarcely ·5 cm. in length,

but that in October, 1904, they had attained a length of 2·5 cm., and were sharply pointed in spite of the removal of the testicles.[1]

A similar observation we had ourselves previously made in the case of an adult cock (of the Plymouth rock variety), which we castrated when two years old. The operation was carried out early in 1902. By November the comb and wattles had shrunken so much that the head was nearly typically female; the neck hackles were thin and weak and ill developed; the sickle feathers of the tail were rather straight, spurs long and sharp.

The bird died in January, 1903. No trace of either testicle was found on careful examination of the abdomen.

In a second case, observed by Professor Watson, a bird, stated to be about nine months old, was shown in the September poultry show at Adelaide, where it looked so well bred that it was bought for breeding. The purchaser found it to be fully potent, but infertile. Professor Watson, suspecting it had been incompletely castrated, opened the abdomen and, finding that this was so, removed some considerable remnants of testicular tissue. About nine days after the operation this bird's comb had lost its brilliancy, and soon began to get definitely smaller.

**(2) Transformation of Plumage of the Male into that of the Female.**

It is only in very rare cases that the male bird acquires the external characters of the female. Under these circumstances, again, the actual degree of transformation varies, and it may, moreover, exhibit a transience, as in the converse case.

Of such transience affecting a limited area we may record the following unique example: A common pheasant, hatched in May, 1902, during the year 1903, and whilst actually under observation and presenting the usual male characters, partially assumed in its tail the typical female plumage. The remarkable fact in the case is that the change did not arise from the simple succession of feathers of female type to those of the male, such as might accompany a moult, but from a transformation of the individual feathers, the distal ends of which retained the male marking, whilst the proximal, growing, portions appeared with the marking peculiar to the hen. We are informed by Mr. Eden Richardson, to whom we owe the gift of the bird, that the change was first noticed about Christmas, 1902, when for

[1] See Addendum at the end of the communication.

about an inch at its base the central tail feather exhibited the hen coloration and marking. The change progressed with the growth of the feather. When the feathers were plucked out, in July, 1903, they were but loosely attached and obviously about to be moulted. One of these feathers is depicted from a coloured drawing made by Mr. Terzi in Plate I.

Since then this bird has passed through two moults, but no female characters have reappeared in the plumage, which during the spring of 1905 was of the fully vivid cock kind. The bird was then unmistakably potent, as it probably was during the season in which its tail feathers underwent the transformation referred to.

A complete transformation of the male plumage into that of the female is excessively rare as a sporadic phenomenon.

Mr. Frank Finn has briefly recorded[1] an example of a hen-feathered bantam cock which he by chance came across. The comb, wattle, and spurs were of the full male size. The bird, which crowed frequently, was of no particular breed and showed no traces of Sebright blood, being single combed and possessing black body plumage and a white bordered neck hackle, without any trace of the black-laced plumage of the Sebright variety. But from such sporadic variations hen-feathered male progeny have in two instances been raised.

### *"Henny game."*

The first of these instances to which we may refer is the breed of "henny cocks" which was raised by Mr. W. B. Tegetmeier from a male bird which sporadically assumed the female plumage. Mr. Tegetmeier has described in the 'Field' (April, 1902) how many years ago he possessed a set of brown-red game bantams with which he won prizes at the Crystal Palace and elsewhere. In moulting after winning at the Palace—*i. e.* in the second or third year—one of these birds assumed the perfect plumage of the hen, which it continued to renew annually until its death, two years later. During the whole of this time it did not become either less combative or less fertile. Mr. Tegetmeier bred from this bird to ascertain what plumage his progeny would assume, with the result that some were normal full-plumaged cocks, whilst others were hen-feathered birds. A figure of the bird (taken from a photograph) is given in the paper

[1] 'Proceedings' of the Zoological Society, vol. ii, 1903.

referred to. It shows a compactly built bird, the right spur, which alone is visible in the illustration, being well developed and sharp; the comb and wattles have been trimmed off; the tail is an elegantly shaped hen's. Unfortunately, no examination of the viscera was made after the bird's death.

Henny game-cocks, for the reason that they retained their combativeness though disguised in female plumage, were highly valued in the prize ring. Whilst as active and vigorous as the normally feathered cock, their feminine appearance, it was said, puzzled their opponents, and threw them off their guard.

In the second instance, the Sebright breed of bantam was raised by Sir John Sebright from crossing into his strain a hen-tailed bantam cock which he casually came across.

With such an absence from the male of birds, of what is commonly the external sexual character, we may associate the fact that amongst certain races of mankind the male is quite devoid, or almost so, of hair on the face, although that of the scalp may be luxuriant.

The male under such circumstances externally resembles the female, much as the henny cocks resemble the hens in the breed of fowls referred to. This, as is well known, is the case in the straight-haired North-American aborigines, in whom the hair of the head is as long in the male as in the female, and may in certain cases attain the length of two metres, whilst the face is practically hairless.[1] In a lesser degree this is true of the straight-haired Mongols, amongst whom the men have hardly more than a rudimentary tuft of beard, although the hair of the scalp is of undiminished length.

As a sporadic congenital variation, apart from the result of disease, complete hairlessness and featherlessness have been observed amongst the lower animals (dog, mouse, domestic fowl) and, in rare cases, in the human subject.

Such examples of universal atrichia or alopœcia, however, have not so direct a bearing on the variations under consideration, since the female may be equally destitute of hair.

### *The "eclipse plumage" in ducks.*

We may conclude this subject of the assumption by the male in birds, of the female plumage, with a reference to the transient

[1] Keane, 'Man Past and Present,' 1900.

phenomenon of an allied kind which occurs regularly in certain kinds of ducks, viz. the seasonal loss of male plumage which is known as "eclipse." Normally in the adult mallard (*Anas bosas*), which, it is assumed, has bred early in the spring, the curly tail feathers are lost, and the moult of the body feathers begins whilst the young are still in down—*i.e.* late in May or early in June. By the beginning of July the assumption of the dusky summer, or "eclipse," plumage should be tolerably complete, though the moult of the flight feathers has not as a rule begun, these being lost usually by the middle of the month. The eclipse plumage persists throughout August, during which month the mallard, the duck, and the young are all very much alike. By the middle of September the curly feathers have usually appeared in the tail of the mallard, and the bird passes from its summer to its winter plumage, which does not, however, reach its maximum beauty until about mid-winter, when the birds begin to pair.

The above account, compiled from the series of wild birds exhibited in the Natural History Museum, South Kensington, on the whole accords closely with the changes observed in a control mallard kept by us with our allopterotic ducks.

The interesting question here arises, How far do the ducks which have assumed the male plumage pass through a similar seasonal eclipse?

Two allopterotic ducks came into our possession during the early spring of 1903, the birds already referred to as coming from Mr. Leno, of Hemel Hempstead. In a general way these suggested the mallard in autumnal or early winter plumage. In both, the curly tail feathers were lost early in June, but no generalised change of plumage comparable to the full "eclipse" ensued; and except for the loss mentioned, both birds continued to resemble the mallard in the manner stated.

One of these birds was killed in July, 1903; the other had regained its curly feathers early in September. The latter bird (No. 36) was not studied during 1904, but came under systematic observation again in March, 1905. Of this, as well as of a further allopterotic duck (No. 33) already referred to as Major Turle's donation, an account of the seasonal change in plumage may now be given. Both these ducks (No. 36, Leno; No. 33, Turle) in a general way resembled the mallard in winter plumage, when they first came into our possession, in February, 1903, and

September, 1903, respectively; and the same applies to the second of Mr. Leno's ducks, which was killed in July, 1903. Since February, 1905, both birds have been under observation in the Zoological Society's Gardens, Regent's Park.[1]

Duck No. 36 (Leno)—In March, 1905, its general appearance was masculine, though not vividly so, its chief peculiarities being that there was little gloss on any of the feathers, whilst there was a brownish tint on the cheeks and neck.

This bird showed no qualitative change in colour until after midsummer; the secondaries of both wings were moulted late in May; the primaries had already, probably, been moulted.

The drake which was kept as a control had on June 13th lost the curly feathers of the tail, and the metallic lustre of the green feathers on the vertex was giving place to dark brown, the chestnut pigment in the feathers on the breast was becoming less brilliant, and here, as in the flanks, a few new feathers were appearing; in short, the eclipse had begun and was everywhere slowly progressing. Of six mallards in St. James's and Hyde Parks, three had lost and three had retained the curly feathers of the tail.

At this date No. 36 (Leno) presented no indications of eclipse. The latter change began early in July, the metallic green of the head feathers being fairly rapidly replaced by a dull brownish tint due to a redistribution or rearrangement of pigment, and not to the growth of new feathers; the scapular feathers and those of the flank exhibited the most obvious change, which was here also due to a pigmentary alteration, and not to a new growth. During July the darkening of plumage progressed but little.

During this period the control mallard passed into complete eclipse. So far, then, although the flanks, scapular feathers, and head became browner than they had been in the spring, the general plumage of No. 36 was predominantly male.

In regard to the control drake, at the end of July it was noted that whilst still apparently in full eclipse, a flush of young vermiculated winter feathers was present in the down beneath the fully developed feathers on the breast and flanks. A slight

[1] We may take this opportunity of gratefully acknowledging the facilities granted us by Mr. R. I. Pocock, the Superintendent of the Society's Gardens, in furthering these investigations.

metallic green tinting was on careful examination recognisable on the vertex. At this time in No. 36 there was a flush of feathers in the down of the flanks and breast, as there was in the control, but the colour of these feathers was for the most part of the dominant, rather dull, hue.

By the middle of August the vertex of the control drake had become greener and more glossy, and this change extended to the neck; on the flanks most of the feathers had become vermiculated, whilst the breast feathers, though darkening, were for the most part still tipped with white; there was no sign of any curling of the tail feathers, but the two central ones had become darker.

In general terms No. 36 presented a similar but less marked alteration; the vertex became somewhat green, as did the cheeks and neck, though to a less pronounced degree than in the control; the feathers of the body were of a greyish-brown, the brownish eclipse-like feathers becoming vermiculated at the tip; the scapular feathers were of a dark grey, mostly vermiculated, tail coverts of a glossy green. The control, by August 30th, had practically assumed its scheme of winter plumage, although the colouring was nowhere typically vivid, and the remains of the eclipse plumage were generally distributed about the body; the head was moderately glossy, though the cheeks were still flecked with brown; a new flush of feathers had appeared on the chest, where, however, a few eclipse feathers still persisted; the new feathers were of a fine dark brown; the belly and flanks were covered with typically male vermiculated feathers, but a few brownish feathers still bore evidence to the late eclipse plumage. At this time the head and neck of No. 36 had become quite as glossy as those parts in the control; the breast was of a rather light chestnut; the belly and flanks were practically as they were in mid-August, although a few more irregularly vermiculated feathers were present, and there were a few well-vermiculated feathers on the shoulders. The condition was practically unaltered on September 9th, and on October 6th the curly feathers of the tail in this bird apparently persisted through the change; that they had been shed and replaced before June is hardly possible.

We may next note what occurred in the duck No. 33 (Turle). Early in September, 1903, when the bird came into our posses-

sion, though it presented the general appearance of an autumn mallard, it differed from the latter in several minor particulars; these were, the only partially glossy green condition of the plumage of the head and neck generally, the presence of a brown area on each cheek behind the eyes, and the brownish tint of many of the flank and belly feathers. In February, 1906, the bird came under systematic observation; its plumage then was in general much as in September, 1903.

Until June 13th, 1905, this bird presented no change, with the possible exception that the vertex was less vivid and the flanks slightly darker.

Between this date and June 23rd the bird lost its old secondaries (and primaries?) in both wings. The head grew browner and less glossy, the eclipse progressing slowly here as it did on the flanks and belly when a few new feathers appeared, the chief part of the colour change being due to a redistribution or replacement of the pigment in the feathers, which redistribution fled to the fine vermiculated black and white coloration of the winter plumage. The result of this process, in the first place, was to cause the ground colour of the hitherto white and black vermiculated feathers to become of a medium brown, whilst the black vermiculations at the periphery of the feather often tended to fade. A certain number of the feathers seemed to remain in this condition for some time, or even indefinitely; in others, the majority, the vermiculations became less definitely arranged, and the black pigment tended to become distributed in irregular flecks and blotches, which caused the old feathers to resemble the new ones of the eclipse plumage.

During July the darkening of the plumage progressed but little; indeed, the white ring around the neck spread somewhat, and flecks of white appeared on the cheeks; one of the curly feathers of the tail became loose and was pulled away. The dominant appearance was, as in No. 36, male. By the middle of August the white ring and flecks on the cheeks were becoming less pronounced; the breast was of a light chestnut, many of the feathers being edged with white; belly feathers greyish-brown, many showing faint traces of vermiculation; on the belly a vigorous flush of young, well vermiculated feathers was appearing at the surface; scapular and interscapular feathers fairly dark brown, becoming obscurely vermiculated; feathers of the lower

part of the back of a metallic green. At the end of August the breast was still of a light chestnut, an abundant flush of young feathers of this colour, often tipped with white, coming through. The flanks and belly remained as in mid-August. The feathers of the shoulders were dark and very irregularly marked. Three old (?) curly tail feathers persisted; these were normally glossy and firmly rooted. September 9th: The green on the head was spreading and becoming more glossy; the fourth tail feather had begun to curl. October 6th: The general character of the plumage had undergone no material change.

We may close these detailed accounts with a third, which concerns a duck deposited in the Zoological Society's Gardens by Mr. W. B. Tegetmeier, January, 1905. This bird is now twelve years old, and was quite fertile until 1903, in which year she laid no eggs. During the spring and summer of 1903 there was no perceptible change in her plumage, but during the autumn moult it was noticed that the feathers on her breast became darker and redder, while her head and neck also changed colour. At the same time her tail feathers began to curl, and the feathers on her back darkened slightly. Her voice remained feminine. No eggs were laid in the spring of 1904, and when she moulted that year it was noted that she assumed to a far greater extent the plumage of the male, and her tail feathers now curled as those of the normal mallard. Early in 1905, when she was sent to Mr. Tegetmeier, her voice was considered to be changing, becoming hoarser and harsher. On the physiological side her behaviour towards the opposite sex was interesting. During the spring of 1903, in which year she laid no eggs, four or five drakes with which she was kept paid her a good deal of attention, as they had in previous years. It was, however, noted that she kept more apart than she had previously done, and in no sense sought their companionship. In 1904, when the drakes neglected her entirely, she for the most part kept to herself, but occasionally trod, or endeavoured to tread, some of the normal ducks with which she was kept. This bird, although mimicking the male, mimics the not very common leaden-coloured variety of mallard. Before the allopterotic change occurred this duck was of a peculiarly light colour, and the wing secondaries were of the peculiarly dull grey that they still are; so that, although the bird has changed its secondary sexual characters for those of the

opposite sex, it has retained the coloration proper to the variety of which it was originally and still is an example.

In January, 1905, the plumage presented by this bird was everywhere of a greyish colour with the exception of the head and breast. As in the mallard of this leaden variety, the breast was of a light chestnut, the head and cheeks brownish-grey, the wing secondaries dull grey.

No change occurred in the plumage during June. On July 22nd there was but one curly feather in the tail (whether old or new was not clear); the head, including the vertex, had become browner, a complete moult of the wing primaries and secondaries was in progress, but there were no young feathers appearing on the body or head. On August 18th there was a complete set of new primaries and secondaries in both wings, and in the tail two curly feathers. There was no flush of young feathers on the breast, but posteriorly where the chestnut tint ended and on the belly the old feathers appeared in part becoming obscurely vermiculated, as they were also on the flanks. On September 1st the vertex was greyish, some of the feathers were tinged with brown; there were a few scattered white feathers on the head and cheeks, the latter being generally of a light brown. The breast was of a rather light chestnut, an abundant flush of young feathers of this colour just tipped with white coming through. The lower part of the chest and the belly were of a dirty greyish-brown, but in the down there was an abundant flush of properly vermiculated feathers. The feathers of the shoulder and flank were the most vermiculated, though even here there was a strong tinge of brown. In the tail there were three well-marked curly feathers, the uppermost grey, the other turning grey from brown, which colour the periphery still was. September 7th: The flush of new feathers were through the down of the belly and definitely though not darkly vermiculated, the general colour of the belly being of a pale grey.

To sum up: In all these birds an incomplete seasonal change occurred. This progressed less rapidly than does the full change in normal males, and evinced a tendency to be irregular in the order in which it occurred. In two of the three birds the wing feathers, which normally should be moulted late, were moulted before the on-coming eclipse had affected the

rest of the plumage, and one of the birds (No. 36) lost its wing feathers as early as May.

On the other hand, the passage from the partial eclipse plumage, assumed by these birds, to their winter dress seems to take place normally (so far as it goes) in regard to order, speed, and season.

The fact that the passage into eclipse in the wild duck coincides with the period of sexual inactivity suggests that a temporary abrogation of glandular function may underlie the production of the external change.

In order to test this we are engaged in observing the results of castration carried out before the advent of the eclipse. Should the latter change be due to the cause suggested, castration would presumably render the eclipse plumage permanent.

Apart from the external, transformation of plumage amongst birds, lesser grades of sexual change may be cited in which the male exhibits only some of the physiological or psychical traits of the hen.

In the spring of 1902 a cock pheasant in the possession of Mr. R. Eden Richardson became broody and sat upon a clutch of eggs from which it drove the setting hen. In the pheasant such an occurrence is highly exceptional, the male being polygamous and leaving the hen as soon as the eggs are laid.

## The Meaning of Allopterotism.

Up to the present it has commonly been held, with Yarrell, that atrophy of the ovary is a sufficient explanation of the phenomenon in which the female acquires the external characters of the male. That the ovary is atrophied in such birds has been observed by various authors, and we are able to confirm the observation in the pheasant and wild duck. Yarrell[1] states that in all the instances examined by him the ovary was shrunken, purple, and hard. The atrophy may exceed what is implied in this description, and as illustrating an extreme degree of it we may introduce a figure from the case of a golden pheasant which we had the opportunity of dissecting through

[1] "On the Change in Plumage of Some Hen Pheasants," 'Phil. Trans.,' 1827, p. 268, and in the abstracts published in the 'Proceedings of the Royal Society,' 1827, p. 317.

the kindness of Mr. W. E. Downing. The bird in question put on the full male plumage after the first moult; it had never laid or shown any sexual instincts. When killed there were no signs of spurs, though it must be remembered that the bird was in no sense an old one.

The ovary in this case is represented by a smooth, slightly elevated, deep black eminence, 1 cm. in length, and 1·5 mm. in breadth where broadest, viz. towards the upper end.

FIG. 23.

A dissection of the viscera of the golden pheasant (*Thaumalea picta*) referred to in the text. The ovary is represented by a smooth, deeply-pigmented, low, oval eminence on the left side, immediately below the left adrenal, and to the inner side of the upper end of the left kidney. (Nat. size. Specimen in the Museum of the Royal College of Surgeons, Physiological Series.)

EXPLICATIO FIGURÆ.

Monstrantur ovarii atrophia et pigmentatio in phasiano (*Thaumalea picta*), in quo notæ masculinæ pro notis femineis substitutæ sunt. Magnitudinis naturalis.

That the ovarian pigmentation is not a necessary accompaniment of the atrophy is shown by its absence in the case of the duck.

Thus in a wild duck received from Mr. W. B. Tegetmeier in March, 1904, in which the male plumage had been completely assumed six years previously, dissection showed the ovary to be a shrunken plaque of tissue 1·5 cm. in length, with minute, sparsely scattered elevations, but devoid of pigmentation.

The same absence of pigmentation we observed also in the atrophied ovary of a second wild duck which had put on the male plumage, viz. one of the two birds received from Mr. Leno of Hemel Hempstead, and already referred to.

In the allopterotic Aylesbury duck, of which the tail is figured on page 83, the ovary was quite devoid of pigmentation both to the naked eye and in microscopic section.

The deep black colour of the atrophied ovary in the pheasant arises from the fact that the gland is normally pigmented, and that in the process of parenchymatous atrophy (*i.e.* the atrophy of the essential or generative elements) the pigment of the stroma becomes concentrated within a smaller area and so intensified. Indeed, in the normal hen pheasant shot in October the ovary is usually quite black, or finely mottled with paler points marking the sites of dormant ova, the ovary being at this season functionless.

The coloration is not confined to the surface, but involves the whole substance of the gland, a microscopic section of which reveals the presence of large numbers of highly irregular, branching cells scattered through the ovarian stroma, and loaded with fine granules of black pigment.

In the male pheasant, also, as might be surmised, pigmentation occurs in connection with the reproductive gland. It is quite common to find the surface of the testicle finely mottled with black. Of several testes examined, however, we have in none seen any pigment in the intertubular connective tissue. The pigmentation is strictly confined to the tunica albuginea. In horizontal sections the pigment appears in the form of narrow, intensely black lines of varying length, disposed circumferentially between the fibres of the tunic; when viewed from the flat the pigment is seen to lie in irregular branching cells, in some of which a nucleus may be discerned, the lines referred to being the sections of extremely flattened cells.

As an histological variation we have once observed pigmentation of the testicle in the chick of the common fowl. Amongst

several birds artificially hatched, and killed on the seventh day, one presented a deeply pigmented testicle; the gland was quite equal in size to its fellow, which was of the usual white colour. Horizontal microscopic sections showed in the tunica albuginea a conspicuous number of intensely black lines of pigment, and a proportional amount of pigment distributed throughout the stroma of the gland in branched and curiously contorted masses; the pigment where least dense was resolvable into extremely minute granules. In the tunica albuginea the lines ran conformably with the elongated cells of the fibrous tissue—*i.e.* circumferentially; the branching forms in the gland-stroma, however, bore no corresponding relationship with the trend of the cells, but ramified independently amongst them; in some there was discernible a comparatively clear oval body representing a nucleus and indicating that the pigment was contained in cells of extremely complex form. In the grouse the stroma of the testicle is strewn with similar fantastic cells.

The hypothesis that the change in external sexual characters is due to atrophy of the ovary and a consequent loss of ovarian function, we regard as inadequate and unsatisfactory, chiefly for the reason that the transformation is not a retrogression, but a progression from a less to a more highly differentiated condition. The hypothesis which we submit, and which we are at present engaged in testing, is that such birds are really bisexual or hermaphrodite—either that the single gland, the "ovary," is bisexual, as in the hermaphrodite fowl described in this communication, or that the sexual gland is paired, one of the paired organs being male and the other female, or that a male element is misplaced and possibly included within a neighbouring viscus like the adrenal or kidney. As age advances, the female gland or the female element of the composite gland retrogrades, upon which the male element, until then quiescent, proceeds to functionate, and with this there comes the striking external transformation in the secondary sexual characters of the bird.

The various grades of such transformation are explicable on the greater or lesser acquirement of glandular function, and the rare cases in which the external change proceeds a certain way and afterwards vanishes, the bird re-acquiring, in whole or in part, its female characters, would admit of a similar explanation —*i.e.* the phenomenon would be related to a corresponding

functional advance and retrogression of the male elements of the glandular apparatus.

It may be pointed out that the presence of a functionating duct in connection with testicular tissue is quite unnecessary for the acquisition of external male characters, and, moreover, that the presence of very little male tissue is sufficient to bring about the result. This our experiments of ligature of the vasa deferentia in the cockerel and Herdwick lamb, and of incomplete caponisation in fowls have shown.[1] Our hypothesis, in short, is that such birds are true hermaphrodites.

As the subject of hermaphroditism is one of great biological interest, and not least so by reason of its bearings on the phenomenon in man, we may briefly state to what degree hermaphroditism has been observed in vertebrates other than birds and mammals.

### Hermaphroditism in Reptilia.

No example of true or glandular hermaphroditism appears to have been observed amongst *Lacertilia*. In the case recorded by Jacquet[2] of a male of *Lacerta agilis*, there was on each side a well-developed oviduct opening above into the general body cavity and below into the cloaca; no ovaries were seen.

Amongst *Chelonia*, Fantham[3] has recently described an instance of true, glandular hermaphroditism in *Testudo græca*. On each side there was a well-developed gonad, that on the left being an ovotestis. The left gland presented an egg 3 cm. in diameter, on the ventral surface of its posterior third; the body in question was proved microscopically to be an ovum. Somewhat exteriorly and dorsally to this ovum, and so within the substance of the left gonad, a second ovum was found in process of development. Furthermore, a few groups of bodies resembling "ovarian ova" were seen scattered in separate groups (follicles) amidst testicular tissue. Both sets of sexual ducts were present.

[1] 'Proc. Roy. Soc. Lond.,' vol. lxxiii, 'Path. Soc. Trans.,' vol. lvi, p. 57.

[2] Jacquet, "Note sur un cas d'hermaphrodisme incomplet chez *Lacerta agilis*," 'Bibliogr. Anat.,' IIIe vol., Paris, 1895.

[3] Fantham, H. B., "On Hermaphroditism and Vestigial Structures in the Reproductive Organs of *Testudo græca*," 'Annals and Magazine of Natural History,' vol. xvi, August, 1905.

In its external characters this tortoise was male, except that the concavity of the plastron, a masculine character, was less marked than in the normal male.

### Hermaphroditism in Amphibia.

Amongst amphibia hermaphroditism is rare. This is particularly the case among the *Urodela*, although Stephan[1] quotes Knappe as speaking of the testes of a salamander in which spermatozoa were to be seen developing in the interior of an egg-follicle, while St. George[2] has described a newt with external male characters, which possessed an ovotestis on each side; in each gland spermatogenesis was actively proceeding, though the ova, which were in varying stages of development, contained no chromatin. Among the *Anura* a fair number of examples have been recorded, notably by Loisel[3] and Marshall,[4] in *Rana temporaria*. Of these, Loisel's specimen is of particular interest, suggesting, as it does, a resemblance to the condition which obtains in the allopterotic birds described in this communication. This specimen, a female frog, presented all the secondary sexual characters of the male; on the right side the ovary was absent; the left ovary was small, contained no ova, and was deeply pigmented. Mr. J. S. Goodall informs us that for many years he has been in the habit of noting aberrations in the sexual apparatus of all the frogs dissected under his direction, but in three only was there an hermaphrodite condition. In the most marked of these a testis lay imbedded in one ovary, the other ovary being normal; ova were present in both oviducts. Externally this frog was female. The testis gave a fluid on scraping, but as no examination was made of the gland or of the fluid, it is uncertain whether at that period the male gland was functionating or not.

Leaving Bidder's organ for the moment out of consideration, glandular hermaphroditism has been described in the toad by

[1] P. Stephan, "De l'hermaphrodisme chez les vertébrés," 'Annales de la faculté des Sciences de Marseille,' tome xii, Fascicule ii.

[2] Quoted by Stephan, *loc. cit.*

[3] Loisel, 'Grenouille femelle présentant toutes les charactères sexuels secondaires du mâle," 'C. R. de la Société de Biologie,' 1901.

[4] Marshall, "On Certain Abnormal Conditions of the Reproductive Organs of the Frog," 'Journ. Anat. and Phys.,' vol. viii, 1884.

Spengel[1] in *Pelobates fuscus* and *Bufo cinereus*. Knappe[2] has seen no fewer than ten examples. With a single exception, in each of the above instances ovaries and testes were present on both sides. In the exceptional case, that of *Pelobates fuscus*, described by Spengel, the posterior half of the left testis was replaced by ovarian tissue presenting the large ova and black pigmentation found in the normal mature ovary. A slighter grade of hermaphroditism, in which more or less advanced, and often degenerate, ova are found between the seminal tubules in sexually active and apparently normal males has been described by Hoffmann,[3] Stephan,[4] and others.

But while the most marked of the above instances of glandular hermaphroditism in the toad bring this animal into line with the other vertebrates in which this phenomenon appears as a rare abnormality, and whilst the slighter cases described by Hoffmann and others seem to anticipate the normal, or almost normal, hermaphroditism of many fish, reference must be made to the special organ present in toads of both sexes, and which is generally held to be a rudimentary, or, more correctly, a retrograded ovary. The fullest account of this—Bidder's organ—is given by Knappe, from whom the following description is taken:

Bidder's organ is found only in the true toads; it persists throughout life in the male, but in the female it retrogrades before sexual maturity is reached; thus, in the females of *B. calamita* it generally disappears in the second year, in those of *B. vulgaris* it retrogrades each winter and develops anew each summer. The organ lies on the ventral surface of the kidney in close relation with the ovary or testis. Shrunken in the spring, it attains its maximum growth towards the end of the summer, at which time it is of a reddish or orange colour and as large as, or larger than, the true testis.

Stephan, who has minutely observed the development of the large cells of Bidder's organ, finds that these are absolutely like the ovarian egg. But although ova are produced both in the ovary and in Bidder's organ, the parenchymatous elements of the latter are more densely packed and exert greater mutual pressure,

[1] Spengel, 'Arbeit. des Zool. Zootom. Institut in Würzburg, Bd. iii, 1876.
[2] Knappe, "Das Biddersche Organ," 'Morph. Jahrb.,' Bd. xi, 1886.
[3] Hoffmann, 'Zeitsch. f. wiss. Zool.,' Bd. xliv, 1886.
*Loc. cit.*

whilst the whole organ, as contrasted with the ovary, is extremely vascular.

In spite of our knowledge of the structure of Bidder's organ, its morphological and physiological significance is still uncertain. Its tissue is generally regarded as ovarian, but Knappe concludes that nothing definite is known as to its significance and function.

That it represents the remains of an originally hermaphrodite gland may, it seems to us, be argued with plausibility since it is present in both sexes, and, according to Knappe, spermatogenesis may be met with in certain of its tubules; and possibly the organ has assumed, or is assuming, the part of a blood-gland engaged in the elaboration of some internal secretion related to sexual development.

It will be seen later, in describing the generative organs of *Myxine*, that we have here to deal, not with a protandric hermaphrodite (as is usually thought), but with an animal in which a single genital gland containing in almost every instance the sexual elements peculiar to both sexes, ripens for only a portion of its length and brings to maturity only the element proper to one sex, the individual being physiologically, therefore, unisexual only.

If now the abortive portion of such a gland were to become highly vascularised (as in Bidder's organ) from its acquiring some vicarious function, it might persist and be transmitted long after the particular animal form in which it arose had passed into some succeeding form in which hermaphroditism (as betokened by a typical ovotestis) no longer existed.

### Hermaphroditism in Fish.

Descending further in the vertebrate series, hermaphroditism is encountered as a variation amongst fish. As such it has been met with in the trout (*Salamo fario*), in the herring (*Clupea harengus*), the cod (*Gadus morrhua*), the mackerel (*Scomber scombrus*).

Of the trout, cod, and mackerel there are examples in the Teratological Series of the Royal College of Surgeons. The anatomical disposition of the gland varies. A certain segment of it may be of the opposite sex (Trout, Spec. No. 711), or

there may be on each side a double gland, of which the testicular element lies by the side of the ovarian (Mackerel, Spec. No. 710).

That such fish may be physiologically bisexual is proved by the first example cited. In this case (as told by the donor, the late Mr. Thomas Andrews, to one of us, C. G. S.), ripe ova and milt were on two occasions extruded from the body by artificial pressure in the manner commonly adopted by pisciculturists; and these "self-fertilised" ova, although kept completely isolated, on both occasions developed normal young. The right generative gland of this specimen appears to be entirely ovarian; the left exhibits near the middle of its length a constricted segment of testicular tissue. In the dog-fish (*Scyllium*) ova have been found in microscopic sections of the testis by more than one observer.

But besides the various foregoing examples of species in which hermaphroditism is so uncommon that it must be viewed as an abnormality, or, more correctly, as a variation, there is a whole series of highly differentiated teleostean fishes in which it is the normal condition.

Syrski,[1] who has carefully investigated the matter, mentions a number of such fishes which are normally or quite commonly hermaphrodite. Such are many sea-perches (*Serranus cabrilla, S. hepatus, S. scriba*), and the Mediterranean gilt-head (*Chrysophrys aurata*)—one of the sea-breams. Other *Sparidæ*, such as *Pagellus mormyrus* and *Box salpa*, he describes as "almost constantly" or "very often" hermaphrodite. In all these species both testis and ovary arise on each side of the middle line from the genital ridge; and whilst in the adult there is for the most part no precise line of demarcation between the testicular and ovarian portions of the gland (*Serranus*), in some species the two portions are separated by a neutral zone containing no differentiated sexual cells (*Chrysophrys*).

Other species occur (such as *Sargus*) in which a moderately advanced bisexual condition of the genital gland is tolerably common. In others (*e. g. Smaris*) the fairly obvious hermaphrodite condition of the genital gland in the young fish becomes less marked as age advances, until it is indicated, perhaps, only by a few degenerate cells proper to the opposite sex, which are

[1] Quoted by Stephan, *loc. cit.*

present in the genital gland of the adult. Here, then, is a condition analogous to that already mentioned, as described by Hoffmann and others in the toad.

### Hermaphroditism in Cyclostomata.

Lowest in the vertebrate series come the Cyclostomata, and amongst these the remarkable hag-fish (*Myxine*). The latter has been the subject of numerous studies. It is commonly held to be a true protandrous hermaphrodite, *i.e.* that in a given individual the sex is male in the earlier periods, female in the later, the gonad producing sperm at one time and ova at another. The latest work by Schreiner[1] on *Myxine glutinosa*, however, seems to show that the condition present is rather comparable to what is described by Stephan in the teleostean *Sargus*, in which an originally undifferentiated germinal ridge gives rise at first to immature products of both sexes, but of which only one series comes to maturity. Whichever of these views may be ultimately adopted, the actual condition of the sexual gland in *M. glutinosa* is as follows: The unpaired genital gland, which is about half the length of the animal, stretches on the right side of the mesentery from the level of the liver in front, to the region of the anus. This gland, a true ovotestis, is ductless, its products being discharged into the belly cavity. The anterior two thirds of the gland, as a rule, are ovarian in function, the posterior third testicular. Between these two portions there may be a sharp line of differentiation, or an intervening transitional zone, in which testicular tissue occupies the free, ventral, edge, whilst the deeper parts are ovarian. More rarely this disposition may be present throughout the length of the gland; or "outliers" of the generative tissue proper to one sex may occur, around the transitional zone, in the main mass of the genital tissue of the other sex; or, lastly, such "outliers" may be present throughout the entire length of the gland.

In the other chief cyclostomatous form, the lamprey (*petromyzon*), ova have been met with in the unpaired testis of the male.[2]

[1] K. E. Schreiner, "Über das Generationsorgan von Myxine glutinosa," 'Biologisches Centralblatt,' vol. xxiv, 1904.

[2] Gadow, "Amphibia and Reptiles," 'Cambridge Natural History,' vol. viii, 1901.

Hermaphroditism, far from being a phenomenon altogether abnormal amongst the higher vertebrates, then, should be viewed, we submit, rather as a reversion to the primitive ancestral phase in which bisexualism was the normal disposition. The apportioning of male and female function to different individuals would, on this view, arise as a later phenomenon in the progress of evolution.

That such a disposition is the primitive one appears from the striking circumstance that in the highest form, the human, both sets of sexual passages are developed in the embryo, and that the reproductive glands in the early phases of development, are undifferentiated from one another.

The philosophical explanation of this morphological truth can hardly be other than that the human form is descended through an hermaphrodite ancestry.

The subject of true hermaphroditism in man has been ably dealt with by Dr. G. F. Blacker and Mr. T. W. P. Lawrence in papers published in the 'Transactions of the Obstetrical Society,'[1] and in the present volume.

As a result of critical examination these authors reduce the number of authenticated—*i. e.* histologically proven—examples to five, inclusive of that described by themselves. Certain others belong without doubt to the same category, but the evidence being only clinical their absolute proof is wanting. In one such, cited by the authors named, the individual menstruated at the age of seventeen years, and cohabited afterwards with a man; at the age of thirty-six cohabitation with both sexes took place; at the age of forty-three the menses ceased, and the individual lived as a male.[2]

The transition of female functions to those of the male in this case tallies in a noteworthy manner with that witnessed in the hens which, after ceasing to lay, acquire the instincts and plumage of male birds.

But the occurrence of true hermaphroditism in man being established, the question arises whether lesser grades do not occur, and whether the fairly common cases in which the human female, after the cessation of menstruation, acquires hair on the

[1] 'Obstet. Soc. Trans.,' vol. xxxviii, 1896.

[2] This case is recorded by Mundé in the 'American Journal of Obstetrics,' vol. viii, 1875–6, p. 615.

face, may not indicate that the retrogression of the ovaries has been succeeded by the progression of some quiescent male tissue.

Still more remote evidence of bisexuality in the human subject may, perhaps, be afforded by the psychical phenomenon of sexual perversion and inversion met with amongst both civilised and savage peoples.

We may, in conclusion, again express our thanks to Mr. W. B. Tegetmeier, to Mr. R. Eden Richardson, and Major Turle for the gift of many of the valuable specimens referred to in our communication, and to Mr. Frank Finn for much information concerning the habits of birds.

## Addendum.

In connection with the phenomenon recorded on p. 89, viz. the continued growth of spurs after castration of the adult cock associated with retrogression of the comb, we may add that the observation agrees with what occurs after castration of the immature bird. We have, in fact, never seen a capon devoid of spurs. When the castration has been incomplete, the whole of the male characters are acquired, but in cases where dissection has shown no remnants of the testicles to have been (unintentionally) left the cockerel has nevertheless grown spurs, although the comb has not advanced beyond that found in the hen. We cannot but conclude, therefore, that this character, commonly regarded as essentially male, is not attributable to the function of the testicle alone, but possibly indicates the concurrent action of some other gland, perhaps the adrenal, seeing that not a few examples of precocious puberty in children have been found associated with adenomatous or carcinomatous growth of the adrenal gland.

(See the paper by Dr. Bulloch and Dr. Sequeira in the fifty-sixth volume of the Society's 'Transactions,' p. 189.)

1905.

## 7. *Leucocythæmia with apparent change of type from spleno-medullary to lymphatic.*

By CHARLES H. MELLAND.

CLINICALLY the distinction between spleno-medullary and lymphatic leucocythæmia is generally perfectly sharp and defined, and easily made. Not only is it that one form is characterised by enlargement of the spleen and the other by enlargement of the lymphatic glands, but the examination of the blood presents an entirely different picture in the two diseases.

*Field I of a stained blood-film from a case of spleno-medullary leucocythæmia.*—There were 460,000 leucocytes in the c.mm., of which 32 per cent. were myelocytes. A typical field contained five myelocytes, each with its round or oval nucleus filling the greater part of the cell and surrounded by "neutrophil" granules. There are six polymorphonuclear "neutrophils," and one cell intermediate between these and the myelocyte type, whilst another apparently similar type of cell has been crushed in preparing the film and the neutrophil granules scattered. There are three eosinophils—two with polymorphic nuclei, one with the large oval nucleus of the eosinophil myelocyte. There is a single "mast"-cell, with rather faintly staining blue granules, and a single "large lymphocyte," with its large nucleus and its narrow zone of rather deeply-staining cytoplasm.

*Field II from a case of lymphatic leucocythæmia.*—In this case there were 658,000 leucocytes in the c.mm., and of these 99 per cent. were lymphocytes, almost all of small size. They resemble very closely the lymphocytes met with in normal blood, being small cells of about the same size as the red corpuscles, with a round, fairly deeply staining nucleus filling the greater part of the cell and surrounded by a narrow zone of cytoplasm staining less deeply than the nucleus, except at its periphery, which is more deeply staining. Many of the cells are very fragile, and liable to be crushed in making the film, and five such crushed cells are visible in the field. Occasional eosinophils and polymorphonuclear "neutrophils" were to be met with. Myelocytes were absent, or only extremely rarely met with.

Thus, the examination of the blood supplies a perfectly sharp line of distinction between the two forms of leucocythæmia, which is quite straightforward and easily grasped. The splenomedullary form is characterised by the enlarged spleen and the presence of a large proportion of myelocytes—myelæmia or myelocythæmia—the medullary cells giving evidence by their presence in the blood, of abnormal action of the bone-marrow, whilst there are also present "mast-cells," nucleated red corpuscles, and a high proportion of eosinophils. In the lymphatic form we find the great preponderance of the cells to be lymphocytes—lymphocythæmia or lymphæmia—coinciding with the enlargement and increased proliferative activity of the lymphatic glands.

Difficulties begin to arise when we turn to the acute form of leucocythæmia. Here, in almost every case recorded, the cells increased have, speaking generally, had the characters of large lymphocytes, and the condition is frequently spoken of as being one of acute *lymphatic* leucocythæmia. But a number of cases of this disease have now been recorded, including one on which I made complete observations in 1899 and published in the 'Medical Chronicle' three years ago (1), in which, with this condition of the blood, the lymphatic glands have appeared normal, the sole lesion being found limited to the bone-marrow, the typical cells of which have been converted into cells more or less closely resembling lymphocytes, the larger forms predominating, and being evidently identical with those of the blood.

*Field III from the above case of acute leucocythæmia.*—There were 105,000 leucocytes in the c.mm., and of these 99·8 per cent. were classed as lymphocytes, the majority of them being distinctly of large size. The characters which these cells presented were a large round nucleus with a rather narrow surrounding zone of cytoplasm, staining less deeply than the nucleus except at the periphery, where, in some of the cells, there was a darker rim. They had thus very much the appearance which one associates with large lymphocytes in normal blood, and have until recently been customarily classified as lymphocytes. There was an almost complete disappearance of all cells with neutrophil and eosinophil granules from the blood. Indeed, at a later stage in the disease a prolonged search failed to bring to light a single specimen. In the field is a single polymorphonuclear neutrophil,

in which the differentiation of the neutrophil granules is very imperfect.

Dr. Parkes Weber (2), in describing a case of acute leucocythæmia in which also the red bone-marrow appeared to be the tissue most affected, the cells in it being converted into lymphoid cells resembling those found in the blood, arrived at the conclusion to which I had arrived, viz. that the lymphocyte-like cells in the blood in acute leucocythæmia originate, in fact, from the cells of the bone-marrow. These cells undergo in the disease in question a degradation in character, losing their highly differentiated capacity of forming granules in their cytoplasm—the neutrophil or eosinophil myelocytes—and returning to the character of indifferent lymphoid cells such as they appear in early embryonic bone-marrow. Billings and Capps (3), in describing the blood and marrow in a similar case, speak not of lymphocytes —which we see is a misleading term, as the cells are coming, not from the lymphatic glands but from the bone-marrow—but rather of non-granular myelocytes.

In another case of acute leucocythæmia that has come under my notice the true character of these lymphocyte-like cells met with in the blood appeared perfectly evident. In this case there was an enormous preponderance of cells, mostly of large size, with round or oval nuclei and a narrow rim of faintly-staining cytoplasm without granules—such cells as have been classified as large lymphocytes, and resembling in their characters those in the field last described. Certain of these cells show a slight diffuse staining of the cytoplasm with the acid dye, whilst occasional ones exhibit the remains of a very few neutrophil granules. It is the presence of these cells, obviously very imperfectly formed myelocytes, which so strongly suggests that the other large cells with exactly similar characters, except for the absence of these very sparse granules, are still more imperfectly formed myelocytes, that these cells are all, indeed, not lymphocytes as has been so generally believed, but, as held by Billings and Capps, highly degenerate forms of neutrophil myelocytes in which the process of differentiation has failed, and that there has resulted the production of a primitive undifferentiated lymphoid cell such as is met with in fœtal bone-marrow.

The recognition of this fact—that the lymphocyte-like cells of acute leucocythæmia are in reality abnormal forms of myelocytes

—is of paramount importance in appreciating the pathological conditions which underlie those rare cases of leucocythæmia which have been described as of a mixed type, a combination of spleno-medullary and lymphatic, or as altering in type, being first spleno-medullary and subsequently becoming lymphatic, of which the following case is an example. I will give a somewhat brief account of the clinical history of the case, going into fuller details concerning the changes in the blood and the pathological changes found in the tissues *post-mortem*.

The patient, a woman aged 35 years, was admitted into the Manchester Royal Infirmary on June 18th, 1904, under the care of Dr. Steell, to whom I owe my best thanks for permission to utilise my observations on the case. Her symptoms had commenced about Christmas, 1903, with weakness and tiredness, and about that time she had some diarrhœa, which latterly gave place to constipation. About four months before admission she noticed swelling of the belly and pain in the left side of it, and two months later her doctor noticed the enlargement of the spleen, which rapidly increased in size in the few weeks before admission.

On admission the spleen was found to occupy practically the whole of the left side of the abdomen, passing down as far as Poupart's ligament, and to the right beyond the middle line.

An examination of the blood on June 21st showed:

| | |
|---|---|
| Hæmoglobin | 44 per cent. |
| Red corpuscles | 2,200,000 per c.mm. |
| Leucocytes | 209,000 per c.mm. |

A differential count of 500 leucocytes gave:

| | | | |
|---|---|---|---|
| Polymorphonuclear "neutrophils" | | 25·8 per cent. | |
| Myelocytes | | 22·2 | „ |
| Lymphocytes | small . 19·8 per cent. | 46 | „ |
| | large . 26 „ | | |
| Large mononuclears | ·2 „ | | |
| Basophils (mast-cells) | | 2·2 | „ |
| Eosinophils | | 4 | „ |

Of the eosinophils $\frac{9}{20}$ were eosinophil myelocytes.

There were sixty nucleated red corpuscles seen, equal to 25,080 in the cubic millimetre, and of these ten were microblasts, fourteen normoblasts, twenty-four megaloblasts, and twelve intermediate.

The examination thus revealed the characteristic blood-picture of spleno-medullary leucocythæmia, with the great increase in the total number of leucocytes, the presence of 22·2 per cent. of myelocytes, and the increased proportion of eosinophils and basophils, and the presence of large numbers of nucleated red corpuscles. The only unusual point was the high proportion of lymphocytes, grouping together under that name all the granule-free mononuclear cells, the aggregate reaching as high as 46 per cent. of the total leucocyte count. To compare this percentage with that of other more typical cases of spleno-medullary leucocythæmia, I have taken the same groups, viz. the large and small lymphocytes and large mononuclears in six other cases that I have examined in the last few months, and these amount to 7, 3, 11·6, 10, 15·6, and 17·2 per cent. in the respective cases, or to an average of about 14 per cent.

Thus, although the blood-picture was in the main that of spleno-medullary leucocythæmia, the presence of this unusually high percentage of lymphocytes stamped it as one of those cases which have been supposed to represent a mixed form of spleno-medullary and lymphatic leucocythæmia.

A careful examination of the stained film revealed the fact, however, that many of these cells classed as lymphocytes—especially the larger ones—were not really lymphocytes at all, although superficially resembling them, but were, as Billings and Capps concluded in their case of acute leucocythæmia, non-granular myelocytes.

*Field IV, from a blood-film of this date.*—Here there are two typical myelocytes with their large, single, round or oval nuclei and their cytoplasm thickly strewn with neutrophil granules, and at the edge of the field are portions of two other such typical cells. There is another cell with a horse-shoe nucleus and neutrophil granules which is one of the intermediate forms between the myelocyte and the polymorphonuclear neutrophil commonly met with in this form of leucocythæmia. The other three cells are examples of the class of corpuscles about the classification and character of which such ambiguity and discussion has arisen. They are cells with a single round or oval nucleus, surrounded by a zone of blue-staining cytoplasm of varying depth, the narrower the zone the deeper being the basophil staining. One of these elements has the narrow,

deeply-staining zone, the other two the broader, less deeply staining one, but there is no absolute distinction between the two types, since on a comparatively limited search every intermediate form between the two may be recognised. They contain no true granules, though in many there is a stippled appearance of the basophil cytoplasm rather suggestive of them.

A careful scrutiny, however, of a number of these cells showed that some of these so-called large lymphocytes contained a few scattered neutrophil granules, and I convinced myself that it was possible to trace every gradation from the granule-free cells to typical myelocytes filled with neutrophil granules. Whilst there appears to be considerable difference in essential characters between typical specimens of myelocytes and large mononuclear cells with basophil cytoplasm, a difference plainly seen on reference to the field last described, there were innumerable intermediate forms to be met with, with both neutrophil granules and basophil stippling, some in which the granules are the more prominent feature, others with well-marked basophil cytoplasm and but few granules.

What, therefore, this high proportion of lymphocyte-like cells —I will, for short, call them lymphoid cells—meant was not that there was in any true sense a mixing of the characters of spleno-medullary and lymphatic leucocythæmia, as other observers have believed, but simply that we had a case of spleno-medullary leucocythæmia to deal with, in which many of the myelocytes turned out by the bone-marrow were so imperfectly developed as to have evolved few or no neutrophil granules in their cytoplasm, and so came superficially to resemble lymphocytes and to produce a condition of the blood mimicking a combination of the two forms of the disease. Even at this date (June 21st) microscopic fields could be found in which the majority of the leucocytes were of this character.

In spite of treatment—she was put on gradually increasing doses of arsenic, though never getting beyond seven minims of Fowler's solution three times a day—she got worse.

The blood on August 2nd showed:

| | |
|---|---|
| Red corpuscles. . . | 2,090,000 per c.mm. |
| Leucocytes . . . | 52,000 „ |

A differential count of 500 leucocytes gave:

| | | | |
|---|---|---|---|
| Polymorphonuclear neutrophils | | | 29·2 per cent. |
| Myelocytes | | | 16·4 „ |
| Lymphocytes | small | 17 per cent. | 48 „ |
| | large | 31 „ | |
| „ | large mononuclears | 0 „ | |
| Eosinophils | | | 5 „ |
| Basophils (mast-cells) | | | 1·4 „ |

Of the eosinophils, nearly one half were eosinophil myelocytes. There were 42 nucleated red corpuscles seen, equal to 4368 in the c.mm., and of these 24 were microblasts, 9 normoblasts, 3 megaloblasts, and 6 intermediate. There was thus a considerable decrease in the total number of leucocytes. The percentage of lymphoid cells had slightly increased, but the proportions of the various corpuscles were not much altered; there was still a considerable percentage of myelocytes, and the granular cells were over 50 per cent.

On August 26th, however, the change in the character of the blood was most striking. The examination on that date showed:

| | |
|---|---|
| Hæmoglobin | 35 per cent. |
| Red corpuscles | 1,820,000 per c.mm. |
| Leucocytes | 42,200 „ |

The differential count gave:

| | | | |
|---|---|---|---|
| Polymorphonuclear neutrophils. | | | 6·2 per cent. |
| Myelocytes | | | 4·8 „ |
| Lymphocytes | small | 37·4 per cent. | 82·8 „ |
| | large | 45·4 „ | |
| Eosinophils | | | 5·4 „ |
| Basophils | | | ·6 „ |

Of the eosinophils, 8 out of 27 were myelocytes. The nucleated red corpuscles were 338 per c.mm., three quarters of those seen approximating to the megaloblast type. There was thus to be noted a progressive diminution of the hæmoglobin and red corpuscles, with a further slight drop in the number of leucocytes. But the most important fact to notice was that the great proportion, nearly 83 per cent., of the leucocytes were lymphoid cells. The polymorphonuclear neutrophils had sunk to 6·2 per cent., and the myelocytes to 4·8 per cent.,

and field after field could be selected under the microscope in which there were none but these lymphoid cells.

*Field V, from a film taken on September 7th.*—This shows the characteristic appearance at this period. A comparison with Field IV shows the extraordinary alteration in the character of the blood in the course of little over two months, an alteration which in similar cases has led other observers to speak of a conversion of spleno-medullary leucocythæmia into lymphatic, but which I am sure we must look on rather as a progressive failure of the bone-marrow to turn out myelocytes fully equipped with neutrophil granules and a more and more complete substitution of degraded, undifferentiated, non-granular cells. At this period the total leucocyte count had fallen to 22,600 per c.mm., and of these 87 per cent. were lymphoid cells, the majority being of large size. The character of these large cells was well pronounced, and it was at once recognised how closely they resembled the cells in the case of acute leucocythæmia described in Field III, which we have already seen reason to consider as non-granular myelocytes. The complete blood-count on this date, September 7th, showed:

| | |
|---|---|
| Red corpuscles | 1,395,000 per c.mm. |
| Leucocytes | 22,600 „ |

Differential count:

| | | | |
|---|---|---|---|
| Polymorphonuclear neutrophils | | | 7·2 per cent. |
| Myelocytes | | | 4 „ |
| Lymphocytes | small | 31 per cent. | 87 „ |
| | large | 56 „ | |
| Eosinophils | | | 1 „ |
| Basophils | | | ·8 „ |

There were 132 nucleated red corpuscles in the c.mm., mostly microblasts. Two out of the five eosinophils were myelocytes.

There is not much further to be said of the clinical history of the case. The patient got steadily worse and died on September 17th.

I may just note as a point of interest that during the last few weeks, when the blood-forming organs were evidently getting more and more functionally defective, as evidenced by the great diminution of hæmoglobin and red corpuscles as well as by the diminution in number and degradation in character of the leucocytes, the spleen became much reduced in size.

The *post-mortem* examination showed changes wholly in keeping with those to be looked for from the conditions observed during life. It is unnecessary to say much about the macroscopic appearances. The liver weighed 50 oz. and the spleen 26 oz. The bone-marrow of the sternum was pale and watery, and the sternum itself was soft and easily crushed, as if from erosion of the bony structures. The lymphatic glands were not enlarged.

Smears of the marrow from the sternum were stained, and sections of spleen, liver, bone-marrow, and lymphatic gland prepared.

The microscopic examination bore out most completely the conclusions at which one had arrived from the consideration of the clinical characters of the blood. The conditions met with in the lymphatic glands and bone-marrow were specially instructive.

The lymphatic glands were not enlarged, and under the microscope the one that was cut showed no evidence of any proliferative activity such as we should have expected had the lymphoid cells in the blood been derived from them. On the contrary, indeed, the sections showed distinctly an atrophic condition. There was thickening of the capsule and increase in the connective-tissue elements of the gland, with diminution in number, and imperfect staining capacity of the round cells over the greater part of it, though here and there islands of gland-tissue, apparently normally provided with cells, were to be recognised.

The bone-marrow showed the absence of the large numbers of neutrophil and eosinophil myelocytes which are normally present. This was specially noticeable on examination of the stained smears from the fresh marrow. Occasional cells with neutrophil or eosinophil granules could be met with, but only after somewhat prolonged and careful search. The majority of the cells of the red marrow had become converted into non-granular cells identical in appearance with the lymphoid cells that were in excess in the blood. The number of nucleated red corpuscles also appeared distinctly diminished. The sections of the bone-marrow show that it has lost its characteristic appearance of a compact tissue made up mainly of large cells, many showing eosinophil or neutrophil granules. It had assumed instead the appearance of an indifferent, undifferentiated lymphoid tissue,

composed of loose, fibrous trabeculæ, in the meshes of which were rather sparsely scattered round cells, both large and small, and red corpuscles.

The spleen showed, like the lymphatic glands, great increase in interstitial tissue and disappearance of the cellular elements or such a degree of necrosis of the cells that they failed to stain. There were occasional eosinophils in the splenic pulp, but there was no evidence, in the presence of numbers of neutrophil myelocytes or nucleated red corpuscles, of conversion of the spleen into a myeloid structure, as has been described in leucocythæmia. The majority of the cells of the spleen were small or medium-sized mononuclear cells.

The liver was highly fatty, the fatty changes being especially marked towards the centre of each lobule. There was a slight excess of rather richly cellular connective tissue in places between the lobules, but no true leucocytic infiltrations, though it is possible that this connective tissue was the remains of such infiltrations which had partaken of the general hyperplasia of the hæmopoietic tissues throughout the body.

Both spleen and lymphatic glands, more especially the latter, showed the presence of numerous bacilli, about the size of tubercle bacilli, which probably represented a terminal infection.

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I have been surprised on looking into the literature of leucocythæmia to find how few of these cases with change of type—whether we consider it real or only apparent—are on record.

Wilkinson (4) describes a case in which at the first examination there were many myelocytes, though even at that date "the lymphocytes were as numerous as myelocytes," and then only eight days later there was pronounced lymphocythæmia, only occasional myelocytes being present.

Seelig (5) reports the blood examination of another case in which the great majority of the cells present were large leucocytes—markzellen—rarely lymphocytes and polymorphs, and only three days later these were replaced by small lymphocytes scarcely larger than red corpuscles.

Van der Wey (6) describes a case with 175,000 leucocytes per c.mm., mostly of large size, the mononuclears in excess, and

all more or less neutrophil, except for a few typical lymphocytes. Three months later the number of leucocytes had risen to 300,000, the majority being then small lymphocytes.

Penzhold and Fleischer (7) describe a case that in August, 1878, was typically splenic leukæmia, but in February, 1880, small lymphocytes constituted the prevailing variety of cell.

In none of these cases do I find any doubt that the cells which were increased in the later stages were of the same nature as the lymphocytes in the ordinary form of lymphatic leucocythæmia, or any suggestion that they might be rather retrogade myelocytes, and products of a highly disordered bone-marrow.

Reimann (8) gives an account of a case in which in the early stages polynuclear neutrophil cells were in excess; later, on account of the rapid progress of the disease, he is of opinion that the blood-forming organs were obliged to supply incompletely developed cells with the production of the appearance of lymphæmia.

Michaelis (9) describes a case in which, with only very slight increase of the leucocytes, there were marked qualitative changes. The vast majority were myelocytes, with only a narrow zone of protoplasm and but few neutrophil granules and cells having all the characters of the lymphoid cells which I have been describing, which, after some discussion, he decides, following Pappenheim, to be incompletely developed myelocytes, and not in any way the same as the lymphocytes of normal blood. The picture of the condition which is reproduced shows a state of the blood closely resembling that described in Field 6 in the present communication.

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8. *Reimann, H.*—Wien. klin. Wochenschr.,' 1899, No. 39.
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## 8. *Hæmatological and chemical observations in a case of spleno-medullary leukæmia under X-ray treatment, with an account of the histology of the hæmopoietic organs after death.*

By J. C. G. Ledingham.

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The following notes are written in continuation of an article on the same subject which appeared in the 'Lancet' of January 14th, 1905 (1). In that article, which included a fairly complete bibliography of radiotherapy in leukæmia down to January, 1905, the effects produced on a male leukæmic patient of 12 years of age by a course of X-ray treatment extending over three months were briefly recorded.

It is proposed here (1) to investigate in more detail the influence of radiotherapy on the blood-picture during the first series of X-ray *séances* from May 17th, 1904, to August 8th, 1904, and during the second series from December 1st, 1904, to March, 1905, when the patient unfortunately succumbed to an attack of influenza.

(2) To record the results of urinary analyses, with special reference to the excretion of uric acid during the high and low leucocyte stages previous to and in the course of the X-ray exposures.

(3) To compare the *post-mortem* appearances and histological findings with those recorded by several observers in experimental animals.

It will be advisable here to recapitulate the main facts of the case. The patient was admitted to the Sick Children's Hospital, Aberdeen, on November 19th, 1902. The spleen was enormously enlarged, its lower border reaching to within a finger's breadth of the pubes, while the anterior border extended two inches beyond the middle line. The blood-picture was characteristic of leukæmia of the spleno-medullary or mixed-cell type.

The red cells numbered 3,570,000, white cells 234,000, with a hæmoglobin percentage of 80. Owing to the patient's idiosyncrasy to arsenic, the only treatment employed was rest and dieting, and for the space of eighteen months the patient led

only a moderately tolerable existence. Face-flushings and difficulties of respiration were often troublesome, and it was found advisable to keep the patient almost entirely confined to bed, as the getting up, even for a few hours, was invariably followed by a rise of temperature. As is frequent in leukæmia, the temperature often arose from no assignable cause. During this time the blood-picture showed little variation. The white cells oscillated round a mean of 200,000, with variations of 40,000 on either side, while the red cells averaged 3,300,000, the ratio of white to red cells remaining at the fairly constant figure of 1 to 15. The red cells also exhibited enormous variations from day to day, a phenomenon to which sufficient attention has not been directed in leukæmia.

I may quote at this point the results of a few representative blood examinations during this period.

November 7th, 1902.—Red cells, 4,056,000; white cells, 260,800; myelocytes, 48 per cent.; polymorphocytes, 39 per cent.; small and large mononuclears, 8 per cent.; mast-cells, 6 per cent.; nucleated red cells, 4 per 100 white cells.

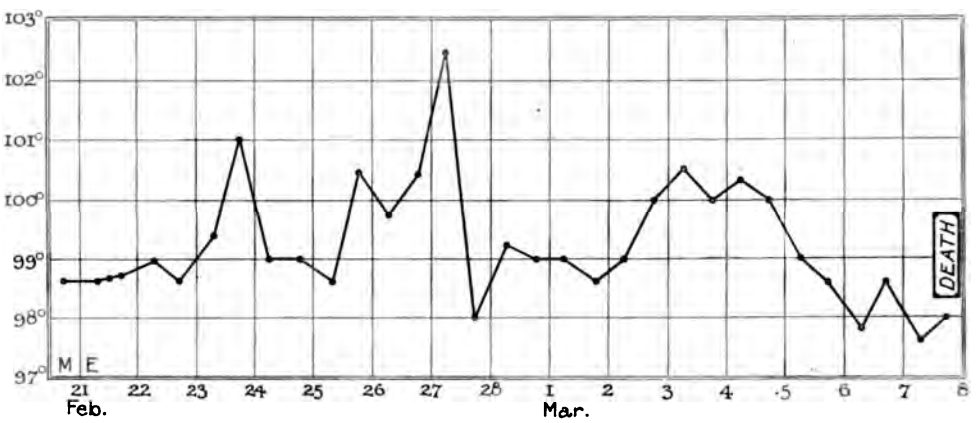
March 24th, 1904.—White cells, 236,800; myelocytes, 56 per cent.; polymorphocytes, 23 per cent.; small and large mononuclears, 17 per cent.; mast-cells, 4 per cent.; nucleated red cells, 3 per 100 white cells.

May 10th, 1904 (exactly a week before the commencement of X-ray treatment).—Red cells, 2,560,000; hæmoglobin, 46 per cent.; white cells, 188,000; myelocytes, 45 per cent.; eosinophil myelocytes, 1 per cent.; polymorphonuclears, 25 per cent.; small and large mononuclears, 21 per cent.; mast-cells, 8 per cent.; nucleated red cells, 8 per 100 white cells.

X-ray treatment was commenced on May 17th, 1904, the exposures being made either daily or on alternate days, for ten to fifteen minutes at a time. The splenic area and the epiphyses of the long bones were the sites usually chosen.

There resulted a remarkable improvement in the patient's general condition, accompanied by very definite changes in the blood-picture which I shall analyse in detail later. The patient was enabled to get up and walk about without the slightest discomfort, while the temperature ran a regular and normal course. The splenic changes were not so striking comparatively as those produced on the blood and the general condition. It was noticed,

however, that after a very few exposures the organ became softer, more palpable, and its edges more readily defined. The abdominal measurements (recorded in the earlier paper) were only very slightly reduced. X-ray treatment was suspended on the 8th August to permit of the patient's going to a convalescent home, where he remained till the end of November, 1904, enjoying the best of health. During his sojourn there blood examinations were made at frequent intervals, and it will be seen from the tables that after the cessation of X-ray treatment the blood-picture showed signs of returning to its former condition. Accordingly, on the 1st of December the X-ray *séances* were resumed. Again there was a very marked re-



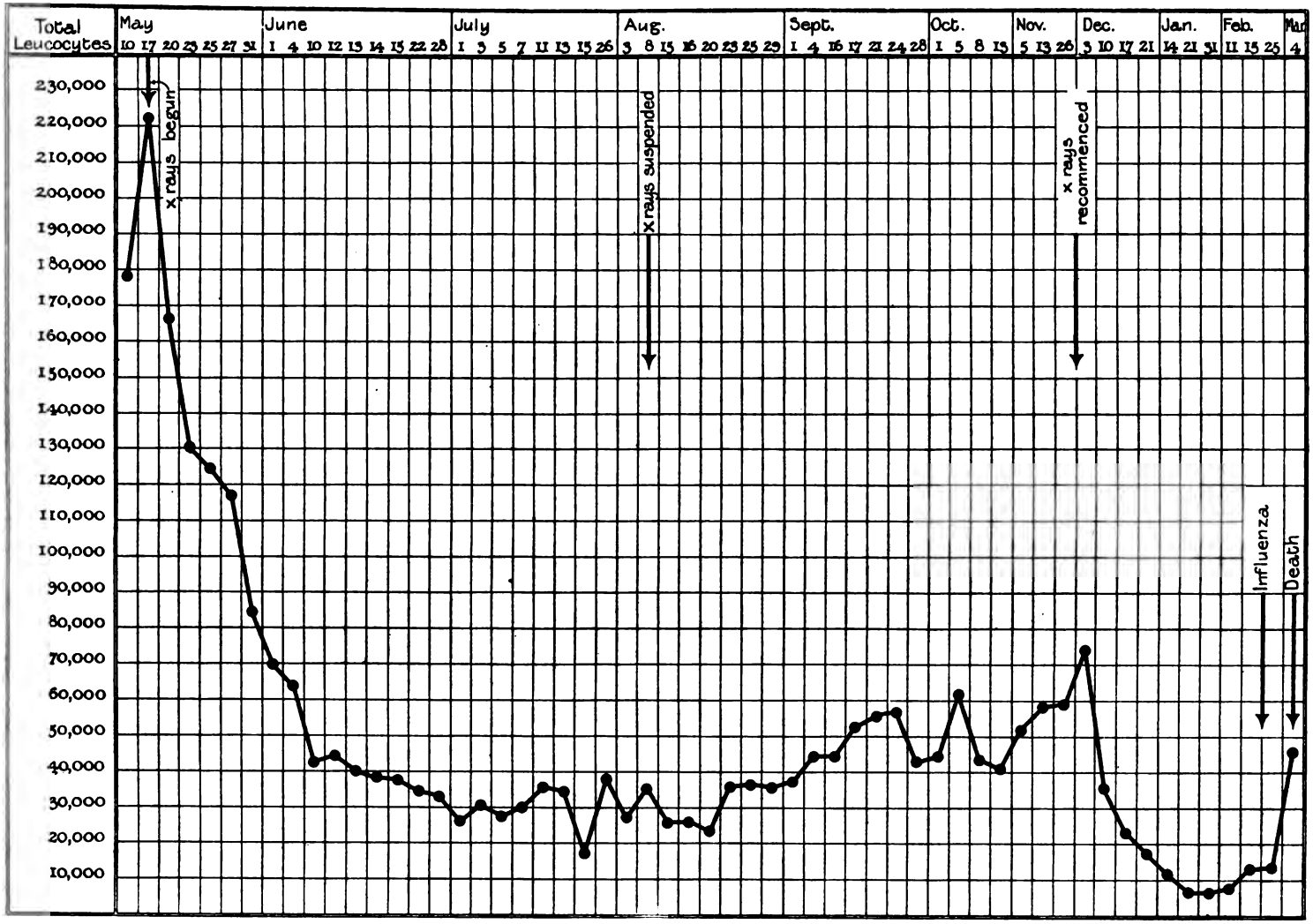

**Temperature chart for the last two weeks of life.**

sponse on the part of the blood elements. In the course of six weeks the leucocytes fell to normal limits, while the temperature ran a consistently normal or subnormal course. Unfortunately, on February 24th a rise of temperature to 101° took place, heralding an attack of bronchitis. The clinical symptoms during the illness were never very pronounced, and the end came rather unexpectedly on March 8th—*i. e.* fourteen days after the commencement of the intercurrent affection. During the last few days cough was distressing and respiration difficult. The temperature chart for the last two weeks is appended. Fortunately, a fairly complete *post-mortem* examination was permitted, and I am indebted to Dr. Duncan, of the Pathological Department, Aberdeen University, for notes of the autopsy and

## EXPLANATION OF CHART I,

Illustrating Dr. Ledingham's communication on a Case of Leukæmia treated by X Rays. (P. 122.)

This chart represents the course taken by the leucocytes from May 17th, 1904, onwards. It will be observed that the leucocytes fell during the first series of *séances* (from May 17th to August 8th, 1904) to a level of 20,000, that during the suspension of treatment from August 8th to December 1st, 1904, they tended to mount slowly upwards in an irregular fashion, and that on the resumption of treatment on December 1st, 1904, they again fell to normal limits. A slight leucocytosis will be observed towards the end, due to the intercurrent infection.


Total Leucocytes
May
10 17 20 23 25 27 31
June
1 4 10 12 13 14 15 22 28
July
1 3 5 7 11 13 15 26
Aug.
3 8 15 18 20 23 25 29
Sept.
1 4 16 17 21 24 28
Oct.
1 5 8 15
Nov.
5 13 26
Dec.
3 10 17 21
Jan.
14 21 31
Feb.
11 15 25
Mar
4
230,000
220,000
210,000
200,000
190,000
180,000
170,000
160,000
150,000
140,000
130,000
120,000
110,000
100,000
90,000
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
x rays begun
x rays suspended
x rays recommenced
Influenza.
Death

for the tissues which were kindly forwarded to me for histological examination.

I now proceed to analyse in detail the changes produced by the X-rays on the cellular elements of the blood.

### (1) The Leucocytes as a Whole.

As the result of the first series of X-ray *séances*, the white cells came slowly down within the space of seven weeks to a level of 20,000 per c.mm. On one occasion the figure 17,800 was reached, but, curiously enough, normal leucocyte limits were not attained in spite of repeated exposures. In fact, this low level of 20,000 appeared to be one of unstable equilibrium, as there was a more or less decided tendency on the part of the white cells to rise even before the cessation of the treatment on August 8th (*vide* Chart I).

The minimum count was reached, as will be seen from the chart, after about seven weeks' exposure—a period corresponding closely with that required to bring the leucocytes to the second minimum during the second series of *séances*.

From the cessation of the first series to the commencement of the second (August 8th to December 1st, 1904) the white cells mounted very slowly upwards in a somewhat irregular fashion to a level of 60,000 or 70,000. It is an exceedingly suggestive fact that the suspension of radiotherapy for three months did little more than raise the total count of white cells to one fourth only of their numbers at the commencement of the treatment. It certainly shows that radiotherapy had exerted an inhibitory influence on the proliferative functions of the blood-forming organs. The peculiar oscillating character of the curve during this period resembles closely that which obtained in the period preceding X-ray treatment.

On the commencement of the second series of *séances* (on December 1st) the leucocytes fell rapidly and progressively to the normal or rather subnormal level of 7000 in the space of six weeks. When this low level had been reached the question of the advisability of continuing the treatment was raised, the risk being that the circulating blood might be completely depleted of leucocytes; and in the light of the recent animal experiments recorded by Halber and Linser (2), to which I shall

later refer, this fear would have been perfectly justified. However, no such effect took place. This low level proved again to be a position of unstable equilibrium, and the white cells rose very slowly to a level of 12,000. It is impossible, however, to say whether the leucocytes would have been retained within normal limits for an indefinite period, owing to the unfortunate intervention of bronchitis leading to the fatal conclusion. One count only was made during the fatal illness, and it was found that the white cells had mounted up to 43,000. The leukæmic leucocytes had, in fact, reacted to the intercurrent infection somewhat more vigorously than normal leucocytes, but in the same direction. Now, it is a well-established fact that intercurrent infections in leukæmia produce a great fall in the number of leucocytes (*vide* Dock's (3) excellent work on this subject), but here in the leucopenic stage of leukæmia the reverse reaction took place.

*Red cells.*

Before the commencement of X-ray treatment the red cells had remained at the fairly constant level of 3,300,000, though remarkable oscillations, upwards or downwards, were frequent within very short periods. It will be seen from Chart II that during the latter part of May, while the leucocytes were progressively diminishing, the red cells showed very little upward tendency. Average for May, 3,383,000.

By the end of June the white cells had almost reached their lowest level, while the average number of red cells for that month had reached only 3,729,000.

By the end of July the leucocytes were already exhibiting a slight tendency to rise again, and this was accompanied by a marked rise of the red cells to an average of 4,264,000.

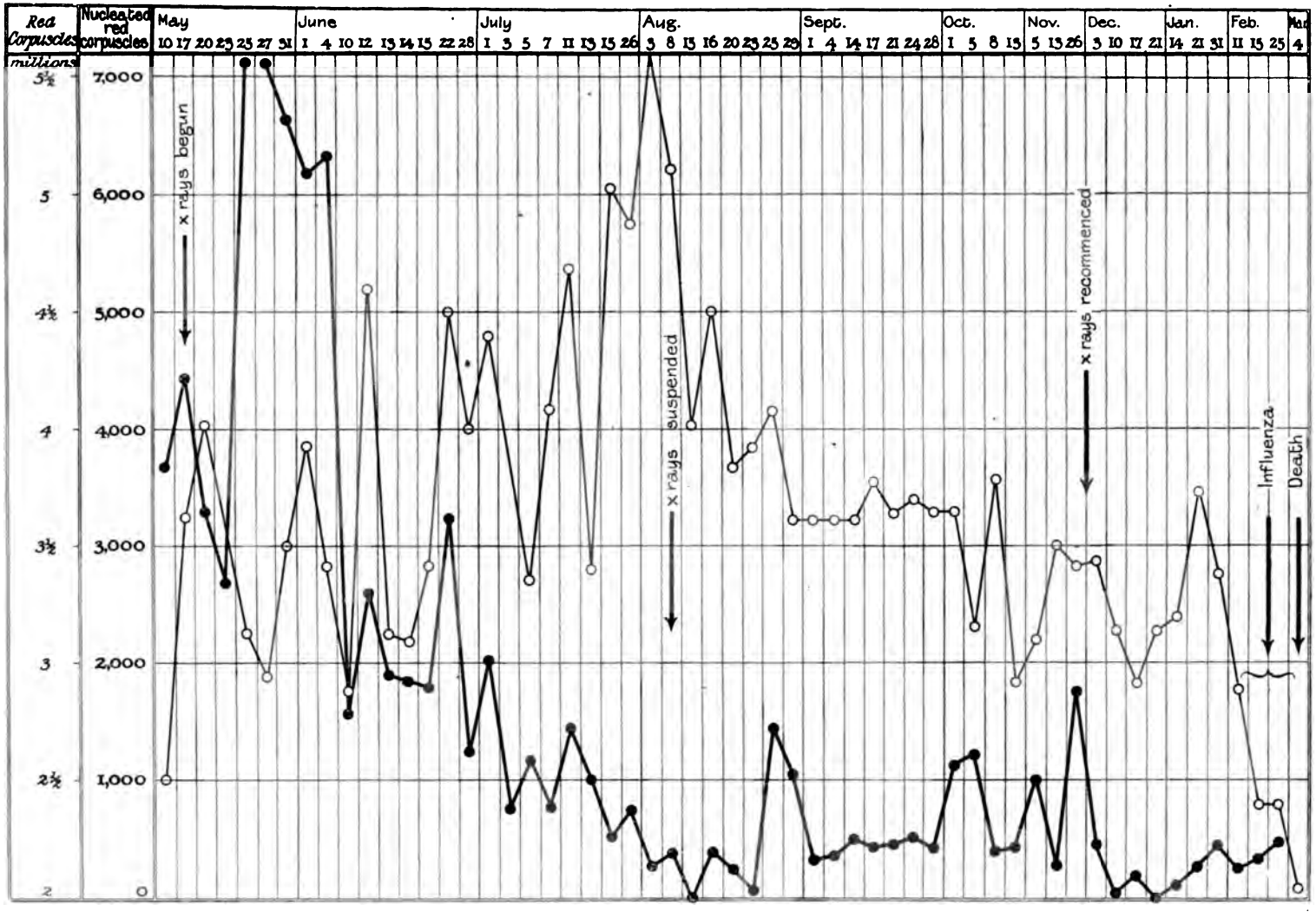
During August, however, when the white cells were quite markedly on the upward stage, the red cells reached their highest level, 4,448,000.

It is curious that the rise of the red cells did not become conspicuous until the leucocytes had reached their lowest level and were already rising again. I observe that in a recent paper by Arneth (4), this feature was also conspicuous. It is possible that the increase of red cells, which is so constant a pheno-

## EXPLANATION OF CHART II,

Illustrating Dr. Ledingham's communication on a Case of Leukæmia treated by X Rays. (P. 122.)

The curves formed by the thick black lines denote the course taken by the erythroblasts, reckoned in absolute values per cubic millimetre. It will be seen that at first these cells respond to X-ray influence by a marked rise in their numbers. Latterly they sink slowly, following closely the course taken by the total leucocytes. The curve formed by the thin black lines denotes the course taken by the red cells. It will be noted that in the first series of *séances* these cells attain their highest limits only after the white cells have fallen to their lowest values. During the suspension the red cells fall slowly, but during the second series another late rise takes place after the white cells have fallen to normal limits. Finally, during the last few weeks very low counts were obtained.


Red Corpuscles
millions
Nucleated red corpuscles
May
June
July
Aug.
Sept.
Oct.
Nov.
Dec.
Jan.
Feb.
Mar
10 17 20 23 25 27 31
1 4 10 12 13 14 15 22 28
1 3 5 7 11 13 15 26
3 8 13 16 20 23 25 29
1 4 14 17 21 24 28
1 5 8 13
5 13 26
3 10 17 21
14 21 31
11 15 25
4
5½
5
4½
4
3½
3
2½
2
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
x rays begun
x rays suspended
x rays recommenced
Influenza
Death

menon in the recorded cases, is not directly due to X-ray influence, as experimental results in animals have shown that these cells make no marked response. The suggestion has been made that the rise of red cells is due to a regeneration taking place as the result of the inhibition of leucocyte production by the rays, or as a consequence of the hæmopoietic organs becoming depleted of white cells.

During September, after the suspension of X-ray treatment, the red cell average fell slightly, and the fall continued during the next two months.

| | | |
|---|---|---|
| Average for | September . | 3,712,000. |
| „ | October . | 3,669,000. |
| „ | November . | 3,349,000. |

The second series of *séances* began on December 1st, and by the end of that month the leucocytes had fallen to 17,000. The red cell average for December was only 3,255,000 however—thus, no improvement. There was a decided, though not very conspicuous, rise in January, the average for that month being 3,543,000. During February and part of March there was a very marked fall in the number of red cells, due, doubtless, to the onset of the fatal illness. Average for February and March, 2,459,000.

It appears, then, that the rise of the red cells (a fact noted by nearly all the observers) does not coincide in time with the fall of the white cells.

### *Hæmoglobin.*

The hæmoglobin was not estimated so frequently as the red and white cells, but sufficient estimations were made to show that during the treatment the percentage bore little relation to the number of red cells in the blood. During May, June, and July the hæmoglobin percentage remained about a level of 45—*i. e.* with an average red cell count of 4,480,000 the hæmoglobin lagged far behind its normal value. Curiously enough, during September, October, November, and December, while the red cells were progressively sinking, the hæmoglobin percentage mounted slowly to 60. During the latter part of January and February, the percentage fell again to 40. In Arneth's case (*loc. cit.*) the same lack of relationship existed between the

hæmoglobin percentage and the red cell count; when the red cells in his case had reached their highest level of 4,272,000, the hæmoglobin estimate was only 61 per cent.

*Effects of radiotherapy on the various leucocyte types.*

The adoption of a satisfactory classification of the leucocytes in leukæmia is an exceedingly difficult matter in view of the extraordinary variety of leucocytes present. This variety extends not only to the well-recognised groups of leucocytes, but to the individual members of each group. The classification of the neutrophile series presents the greatest difficulty, owing to the large number of transition forms between the typical myelocyte and the fully formed polynuclear cell.

Arneth (5) offers an exceedingly refined classification of the neutrophile cells. No fewer than five main types are distinguished, and these are again subdivided according to the number and windings of the nuclei and other minute details. It is questionable if much is gained thereby. The old classification into polynuclears and myelocytes was considered quite sufficient, while the transition forms were classed as polynuclears or myelocytes according as their morphology approached more or less closely one or other of these two groups.

It will be convenient to consider the polynuclears and myelocytes together. Before the commencement of radiotherapy the differential counts showed a marked predominance of the myelocyte percentage over those of the other varieties. The ratio of polynuclears to myelocytes was on an average 1 : 2. Very soon, however, after the commencement of the treatment the polynuclear percentage commenced to rise, the rise continuing during the period when the total leucocytes were sinking.

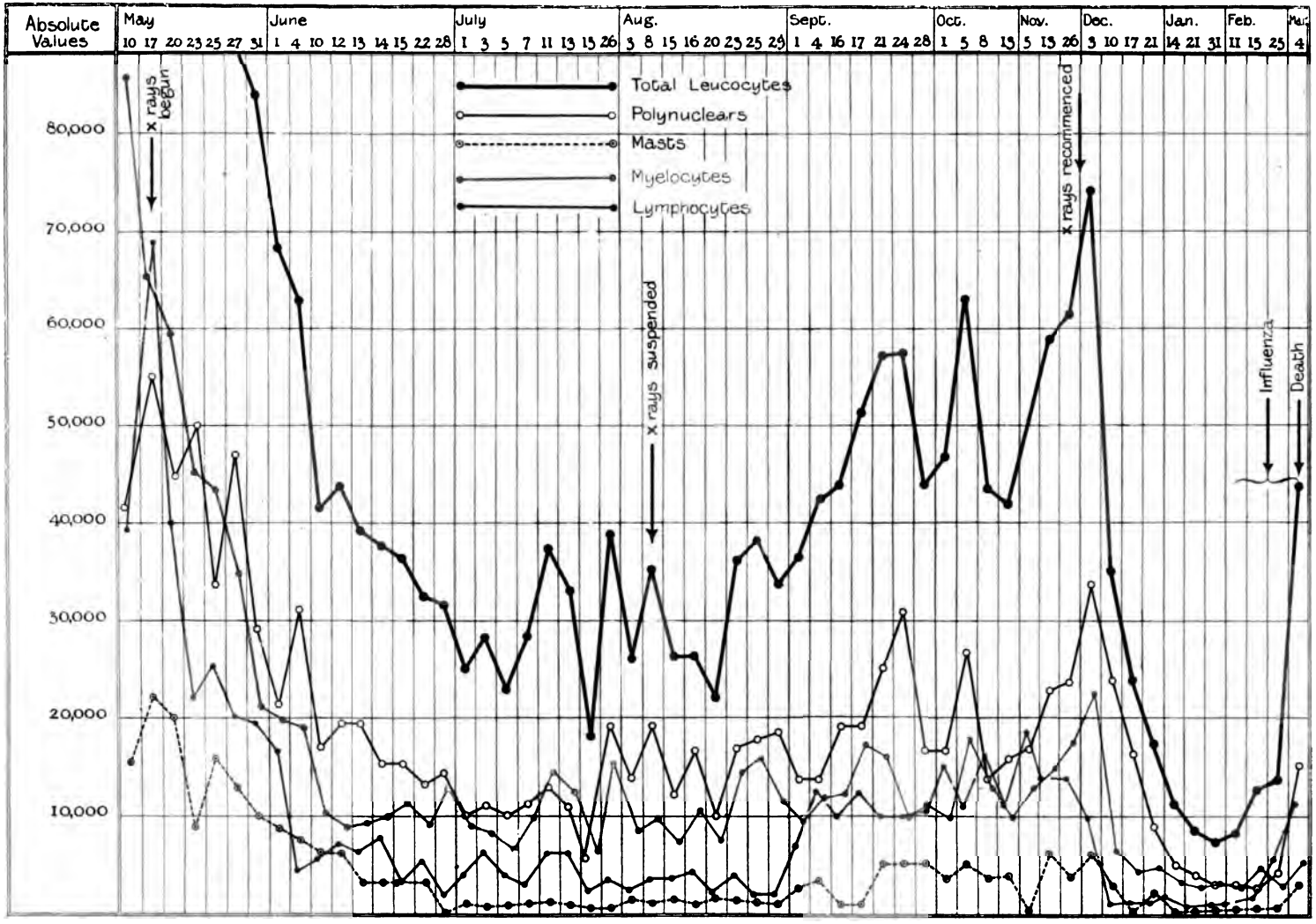
In Chart III the absolute values only of the different cell types are represented, but here I shall refer more particularly to the percentages.

The following table shows the average percentages of the polynuclears, myelocytes, and lymphocytes calculated from the counts made during the months May, 1904, to March, 1905:

## EXPLANATION OF CHART III,

Illustrating Dr. Ledingham's communication on a Case of Leukæmia treated by X Rays. (P. 122.)

This chart denotes the course taken by the different types of leucocytes, expressed in absolute values per cubic millimetre. It will be observed that shortly after the commencement of X-ray treatment the myelocytes lose their position as the predominant white cells, the polynuclears taking first place. As the total leucocytes fall, the cells of the neutrophile series (polynuclears and myelocytes) fall much more slowly than the cells of the non-granular or lymphocyte series, which are most susceptible to the rays. The result is a relative increase of neutrophile cells, especially of the polymorphonuclear variety. During September, October, and November the lymphocytes again mount upwards, to fall again rapidly during the second series of *séances*. Towards the end the lymphocytes again rise to the second place. The mast-cells, after a slight initial rise, fall slowly, following the general curve of the leucocytes.


Absolute Values
May
10 17 20 23 25 27 31
June
1 4 10 12 13 14 15 22 28
July
1 3 5 7 11 13 15 26
Aug.
3 8 15 16 20 23 25 29
Sept.
1 4 16 17 21 24 28
Oct.
1 5 8 15
Nov.
5 13 26
Dec.
3 10 17 21
Jan.
14 21 31
Feb.
11 15 25
Mar.
4
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
x rays begun
Total Leucocytes
Polynuclears
Masts
Myelocytes
Lymphocytes
x rays suspended
x rays recommenced
Influenza
Death

| | Lymphocytes. | Polynuclears. | Myelocytes. | Total neutrophile percentage. |
|---|---|---|---|---|
| May | 22 | 31 | 33 | 64 |
| June | 15 | 43 | 29 | 72 |
| July | 16 | 42 | 35 | 77 |
| August | 9 | 51 | 34 | 85 |
| September | 24 | 42 | 27 | 69 |
| October | 29 | 37 | 24 | 61 |
| November | 28 | 38 | 24 | 62 |
| December | 9 | 60 | 21 | 81 |
| January | 21 | 46 | 28 | 74 |
| February | 37 | 24 | 22 | 46 |
| March | 31 | 35 | 23 | 58 |

It will be seen that by the end of May the polynuclears have become the predominant cells, which they continue to be till the end of January, 1905. The rise of the polynuclears during the first series of *séances* takes place mostly at the expense of the lymphocyte series but also partly at the expense of the myelocytes. Thus the total neutrophile percentage mounts progressively from 64 in May to 85 in August, when a fall takes place coinciding with the suspension of the rays. Arneth also showed that the total neutrophile cells, including polynuclears, myelocytes, and transition forms, increased during the period of fall of the total leucocytes. After the suspension of the rays on August 8th a marked rise in the lymphocyte percentage took place, and during the next three months the percentage continued in spite of slight oscillations to rise till the latter part of November, when on one or two occasions their percentage exceeded even that of the polynuclears.

On the commencement of the second series of exposures on December 1st the great rise in the polynuclear percentage which took place was associated with a tremendous fall in the lymphocyte percentage, but the change was only a transitory one. In January the polynuclears, though still remaining the predominant cells, experienced a marked fall relatively to the other cells. The myelocytes were only slightly affected, and consequently the lymphocyte percentage progressively rose till the conclusion of the case. The last count, however, showed that the terminal leucocytosis was a polynuclear one. These interesting relationships of the three chief varieties of cells will demand our attention later in the light of the *post-mortem* findings.

No very definite statements can be made regarding the variations of the eosinophile series owing to the very small numbers of these cells present throughout the whole history of the case.

*Mast-cells.*

The mast-cells were notably influenced by the treatment. Their average percentages during the months May, 1904, to March, 1905, were as follows:

| | | | |
|---|---|---|---|
| May . . | 11 per cent. | November . | 7 per cent. |
| June . . | 10 „ | December . | 9 „ |
| July . . | 4·5 „ | January . | 4 „ |
| August . | 5 „ | February . | 7 „ |
| September . | 8 „ | March . . | 10 „ |
| October . | 8·5 „ | | |

It will be seen that during the first two months the mast-cell percentage is very slightly influenced, some of the individual counts showing even a very decided rise above the original figure before treatment. In July and August, however, the percentage fell markedly, only to rise again after the suspension of the rays. The same phenomenon occurred during the second series, the second minimum appearing in January, while the December average was even higher than that for November.

An initial rise in the percentage of mast-cells has also been noted by Arneth (*loc. cit.*) and by Joachim and Kurpjuweit (6).

*Nucleated red cells.*

The variations which these cells underwent were somewhat similar to those of the mast-cells (*vide* Chart II).

The figures for the different months were as follows:

| | |
|---|---|
| May . . . . | 4 per 100 leucocytes. |
| June . . . . | 6·5 „ |
| July . . . . | 4 „ |
| August . . . | 1·5 „ |
| September . . . | 1 „ |
| October . . . | 1·5 „ |
| November . . . | 3 „ |
| December . . . | 0·3 „ |
| January . . . | 5 „ |
| February . . . | 4 „ |
| March . . . . | 5 „ |

It will be seen that after an initial rise the nucleated red cells reached their lowest limits in August, September, and October, when the red cells had attained their maximum limits. In January and February another rise took place when the red cells were slowly diminishing.

Practically all the nucleated red cells met with belonged to the normoblast type. In the films for December and January, however, an occasional megaloblast exhibiting karyokinesis or karyorrhexis was observed.

Having now discussed the blood-changes, we may here briefly refer to some of the recent papers dealing with the hæmatology of the subject. The experiments of Heineke (7) are already well known. He showed that the exposure of small animals (mice) to the X rays led to a destruction of the lymphoid cells in the spleen follicles and lymph-glands. The nuclear *débris* was taken up by phagocytes, and finally the follicles disappeared, their places being taken by epithelioid cells and fibrous tissue. Further, after more prolonged exposure to the rays, the specific cells of the marrow were in great part destroyed. These results have so far only been partly confirmed. Joachim and Kurpjuweit (*loc. cit.*) were unable to demonstrate these changes in the lymphoid organs described by Heineke, but Milchner and Mosse (8) have found that exposure of the rabbit's marrow to the rays leads to great destruction of myeloid cells, while those that survive exhibit a great deficiency of granules. The lymphoid cells of the marrow also disappear, but the red blood-cells are not affected. Hynek (9), however, records improvement in a case of pernicious anæmia treated by the X rays, while Vaquez and Laubry (10) found no reduction in the red cells in polycythæmia so treated. In view of the experimental results, it seems difficult to explain the almost invariable increase of red cells that occurs during radiotherapy in medullary leukæmia. In cases of lymphatic leukæmia recorded by Schenck (26) and Joachim and Kurpjuweit (*loc. cit.*) the red cells either diminished or remained stationary.

Wendel (11) believes that the X-rays have no direct action on the red-cells, but that these increase by a process of regeneration consequent on destruction of the white cells in the blood-forming organs.

Arneth (*loc. cit.*) lays stress on the fact that in many of the

cases treated the spleen alone has been exposed, while the same favourable results were obtained regarding the red cells. In his opinion the X-ray treatment of leukæmia is probably directed towards the destruction of some hypothetical parasitic agent, as was thought also by Senn and Ahrens.

A good deal of light has been thrown on the subject by the experimental results of Halber and Linser (*loc. cit.*). Rats, rabbits, and dogs were exposed to the X rays, and in the case of rats it was found possible to deplete the circulating blood entirely of leucocytes in five to ten hours. After seventy hours the circulating blood of rabbits was almost free of leucocytes, though sometimes counts lower than 1500 or 2000 were not recorded. The larger the animal the more difficult it was to effect a complete depletion of the circulating leucocytes. The hæmopoietic organs of animals killed during the low leucocyte stage were examined, and it was found that the diminution of leucocytes in the circulating blood was not due to retention of these cells in the organs. In films, however, he observed signs pointing to an actual destruction of leucocytes in the circulating blood, such destruction affecting principally the lymphocytes. Their nuclei were pale, diffusely stained cells were often met with, and the nuclei of polymorphonuclear cells had sometimes completely disappeared. He found that the rays had only a very slight destructive influence on the red cells, blood-plates, and hæmoglobin. Some of the animals which died after prolonged exposure presented changes in the kidneys pointing to acute nephritis. Such changes he attributed to the action of leucotoxines set free from the broken-down leucocytes. He found further that the serum of animals exposed to the X-rays had a leucotoxic action when injected into fresh animals. This Röntgen serum was rendered inactive by heating to 55°–60°.

From the recorded cases of leukæmia treated by the X rays evidence of leucocyte destruction in the circulating blood is not forthcoming, but the results of Halber and Linser are sufficiently remarkable in themselves. As yet they lack confirmation. Grawitz alone, in a case of chronic leukæmia of lymphatic type which reacted successfully to the X rays, inclined to the view that possibly a destruction of cells took place in the circulatory blood, or that some changes occurred in the blood which led to a premature dissolution of inherently weak cells.

This observer also X-rayed leucocytes in hypertonic and hypotonic salt solutions, and found that the lymphoid cells broke down very quickly after exposure, though previously they had been quite resistant.

A very complete account of the relations of the leucocytes during radiotherapy is given by Franke (12). Regarding the mast-cells, he noted that on the day after the first sitting they diminished greatly in number, but from the second day the number always rose. At the end of the observation period the mast-cells even exceeded the myelocytes. They regard it as impossible to believe that destruction of white cells takes place in the circulating blood as Halber and Linser maintain. Nor do they think that leucotoxines play a part in the process, for they found that serum from a case of leukæmia under treatment dissolved neither normal nor leukæmic leucocytes.

## Part II. Urinary Analyses.

I shall now detail as briefly as possible the results of the urinary analyses made during the progress of this case before and after the adoption of X-ray therapy. During the five months preceding the X-ray treatment frequent analyses of the uric acid output were made, with a view to determining whether, according to Horbaczweski's (13) theory, any relationship could be found between variations in the purin output and the leucocyte count. At the same time, estimations of the total nitrogen were made, so that the nitrogen content of the uric acid might be compared with the total nitrogen excreted. Towards the latter part of the series of investigations the phosphoric acid output was estimated in addition. The technique employed was, briefly, as follows: The total nitrogen was estimated by Kjeldahl's method. The distillate was received in a decinormal solution of pot. tetraoxalate, which was then titrated with caustic soda, phenolphthalein being employed as indicator. The uric acid was estimated by Hopkins' method. The ammonium urate precipitate was treated with hydrochloric acid, and the resulting yield of uric acid received on a weighed Gooch crucible and filtered *in vacuo*. After the precipitate had been washed with carbon disulphide and ether, the crucible was dried in the air oven to constant weight.

The phosphoric acid was estimated by the usual uranium method, tincture of cochineal being employed as indicator. The total daily urine was carefully measured, and the samples for analysis taken from the mixed urines.

Before commencing this investigation it was anticipated that a stage in the progress of the disease might supervene in which the leucocytes might show a progressive tendency to diminish, so that one might definitely demonstrate whether a simultaneous rise of the uric acid pointed to leucocyte destruction. As already noted, however, no progressive diminution took place in the total leucocyte count, although marked oscillations were frequent. When ultimately, under the influence of the X rays, the leucocytes did show a tendency to sink progressively to normal levels, the period when the white cells had sunk to about 40,000, and were still sinking, was considered suitable for the execution of a further short series of urinary analyses on successive days.

Most of the workers in this field of research have been unanimous in finding an absolute increase in the amount of uric acid in the urine of patients suffering from myelogenous leukæmia, but the few accurately-recorded comparative estimations of the uric acid output and the total leucocyte count have yielded only very variable results, and only occasionally could any decided correspondence between a rise in the uric acid and a fall in the total leucocytes be demonstrated.

Giraudeau (14) (1884) found an increase in the uric acid to four times its original amount during a period when the leucocyte count was sinking.

Sticker (15) (1888) found, on the other hand, a rise in the uric acid simultaneously with a rise in the leucocyte count.

Wey (16) (1896) found the uric acid absolutely increased. The uric acid and total nitrogen rose simultaneously along with an increase in the amount of urine. No relationship could be found between the leucocyte count and the uric acid output.

Milroy and Malcolm (17) found a low $P_2O_5$ excretion in medullary leukæmia. The retention of phosphorus they attributed to a diminished leucolysis. Again, in a case of myelogenous leukæmia, where the leucocyte count was diminishing, they found the absolute excretion of $P_2O_5$ relatively high, although its proportion to the total nitrogen was rather lower than normal. The alloxuric excretion underwent marked variations.

As the investigations extended over a very long period, it was found impossible to regulate the diet so that it should be entirely purin-free. Weighed quantities of bread, milk, and eggs formed, however, the staple diet, while a very small amount of flesh food was allowed at the midday meal. Calculated from König's tables, the average amount of nitrogen ingested per day was about nine grammes, but it varied slightly from day to day. To obviate any errors that might arise from small quantities of exogenous purins in the diet, control urinary analyses were made on several occasions on bedridden patients of the same age and weight as the leukæmic case, and who were receiving the same diet. These controls were generally tolerably healthy, but still bedridden, convalescents whose powers of food assimilation were presumably equal to those of our patient.

TABLE I.

| Date. | Total daily urine. | Specific gravity. | Total uric acid. |
|---|---|---|---|
| 1903 | | | |
| November 18 | 820 | 1024 | ·65288 |
| „ 19 | 530 | 1023 | ·4664 |
| „ 20 | 400 | 1026 | ·3464 |
| „ 22 | 400 | 1026 | ·3704 |
| „ 23 | 600 | 1026 | ·5514 |
| „ 24 | 600 | 1026 | ·5034 |
| „ 25 | 400 | 1029 | ·2412 |
| „ 26 | 550 | 1026 | ·38005 |
| „ 29 | 700 | 1024 | ·7721 |
| Average | 555 | 1025 | ·4760 |
| December 1 | 570 | 1028 | ·65379 |
| „ 3 | 550 | 1025 | ·52965 |
| „ 6 | 550 | 1025 | ·5709 |
| „ 8 | 400 | 1027 | ·3596 |
| „ 13 | 650 | 1026 | ·6227 |
| „ 14 | 400 | 1024 | ·3668 |
| Average | 520 | 1026 | ·5172 |

In Table I are recorded the results of fifteen estimations of the uric acid output during the months of November and December, 1903. It will be seen that though there are considerable variations in the amount of uric acid passed from day to day, the average total is considerably above that for a healthy

individual of the same age. Thus, on December 3rd, while the leukæmic patient excreted ·52,965 gram uric acid with 550 c.c. urine, the control excreted only ·2360 gram uric acid with

TABLE II.

| Date. | Total daily urine. | Specific gravity. | Total nitrogen. | Total uric acid. | Percentage of uric acid nitrogen in the total nitrogen. | Total $P_2O_5$. | Ratio of $P_2O_5$ to total nitrogen. | White cells. | Red cells. | Ratio of white to red. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1904 | | | | | | | | | | |
| Jan. 7 | 320 | 1028 | 3·9568 | ·32736 | 2·2 | — | — | 254,000 | 3,336,000 | 1 : 13 |
| „ 12 | 400 | 1026 | 3·248 | ·5204 | 5 3 | — | — | — | — | — |
| „ 14 | 400 | 1023 | 4·928 | ·452 | 3 | — | — | 249,200 | 2,872,000 | 1 : 11 |
| „ 17 | 560 | 1026 | 7·5264 | ·64064 | 2·8 | — | — | — | — | — |
| „ 19 | 380 | 1028 | 3·6176 | ·45562 | 4·2 | — | — | 246,400 | 3,448,000 | 1 : 13 |
| „ 21 | 550 | 1027 | 5·544 | ·55275 | 3·1 | — | — | 198,400 | 3,248,000 | 1 : 16 |
| „ 24 | 600 | 1023 | 7·224 | ·6132 | 2·9 | — | — | 240,800 | 3,184,000 | 1 : 13 |
| „ 26 | 520 | 1027 | 6·2608 | ·63804 | 3·3 | — | — | 245,200 | 3,320,000 | 1 : 13 |
| Average | 466 | 1026 | 5·2882 | ·5250 | 3·35 | — | — | 239,000 | 3,234,000 | — |
| Feb. 1 | 480 | 1030 | 6·048 | ·58368 | 3·2 | — | — | 215,600 | 2,904,000 | 1 : 13 |
| „ 5 | 380 | 1029 | 4·8944 | ·4199 | 2·9 | — | — | 172,000 | 2,768,000 | 1 : 16 |
| „ 9 | 650 | 1026 | 6·188 | ·78 | 4·2 | — | — | 223,600 | 3,408,000 | 1 : 15 |
| „ 15 | 450 | 1029 | 5·292 | ·4734 | 2·9 | — | — | 166,500 | 2,896,000 | 1 : 17 |
| „ 19 | 580 | 1022 | 6·9832 | ·66062 | 3·1 | — | — | — | — | — |
| „ 23 | 640 | 1024 | 4·8384 | ·66112 | 4·5 | — | — | 209,600 | 3,944,000 | 1 : 18 |
| „ 25 | 340 | 1027 | 3·332 | ·56610 | 5·6 | — | — | 173,200 | 3,464,000 | 1 : 20 |
| Average | 502 | 1026 | 5·3680 | ·59211 | 3·8 | — | — | 193,400 | 3,230,000 | — |
| Mar. 1 | 480 | 1027 | 3·8976 | ·44352 | 3·8 | — | — | 151,600 | 4,200,000 | 1 : 27 |
| „ 8 | 620 | 1029 | 3·8192 | ·8587 | 7·4 | 1·5996 | 1 : 2 | 140,000 | 3,184,000 | 1 : 22 |
| „ 9 | 550 | 1029 | 6·314 | — | — | 1·287 | 1 : 5 | 117,600 | 3,200,000 | 1 : 27 |
| „ 10 | 310 | 1029 | 3·6456 | ·46655 | 4·2 | ·6448 | 1 : 5 | 134,400 | 3,416,000 | 1 : 25 |
| „ 15 | 530 | 1025 | 5·6392 | ·32489 | 1·9 | ·5194 | 1 : 10 | 198,000 | 4,160,000 | 1 : 21 |
| „ 22 | 650 | 1026 | 9·1 | ·58825 | 2·1 | 1·82 | 1 : 5 | 233,200 | 3,416,000 | 1 : 14 |
| „ 23 | 480 | 1027 | 6·72 | ·57072 | 2·8 | 1·344 | 1 : 5 | 170,800 | 3,272,000 | 1 19 |
| „ 24 | 550 | 1028 | 7·7 | .814 | 3·5 | 1·21 | 1 : 6·3 | 236,800 | — | — |
| „ 25 | 500 | 1029 | 4·62 | — | — | ·79 | 1 : 6 | 186,800 | 3,120,000 | 1 : 17 |
| „ 31 | 700 | — | 6·944 | ·7327 | 3·5 | 1·2236 | 1 : 5 | 193,600 | 3,616,000 | 1 : 18 |
| Average | 537 | 1027 | 5·840 | ·5991 | 3·6 | 1·1598 | 1 : 5·4 | 176,280 | 3,509,000 | — |
| April 1 | 620 | — | 6·6416 | ·63835 | 3·2 | 1·3032 | 1 : 5 | — | — | — |
| „ 11 | 540 | — | 6·4176 | ·63317 | 3·2 | 1·262 | 1 : 5 | 194,000 | 3,240,000 | 1 : 17 |

800 c.c. urine, a figure which is never reached by the leukæmic patient throughout the whole series.

The urinary estimations for the next four months are recorded in Table II. During January and February the total nitrogen

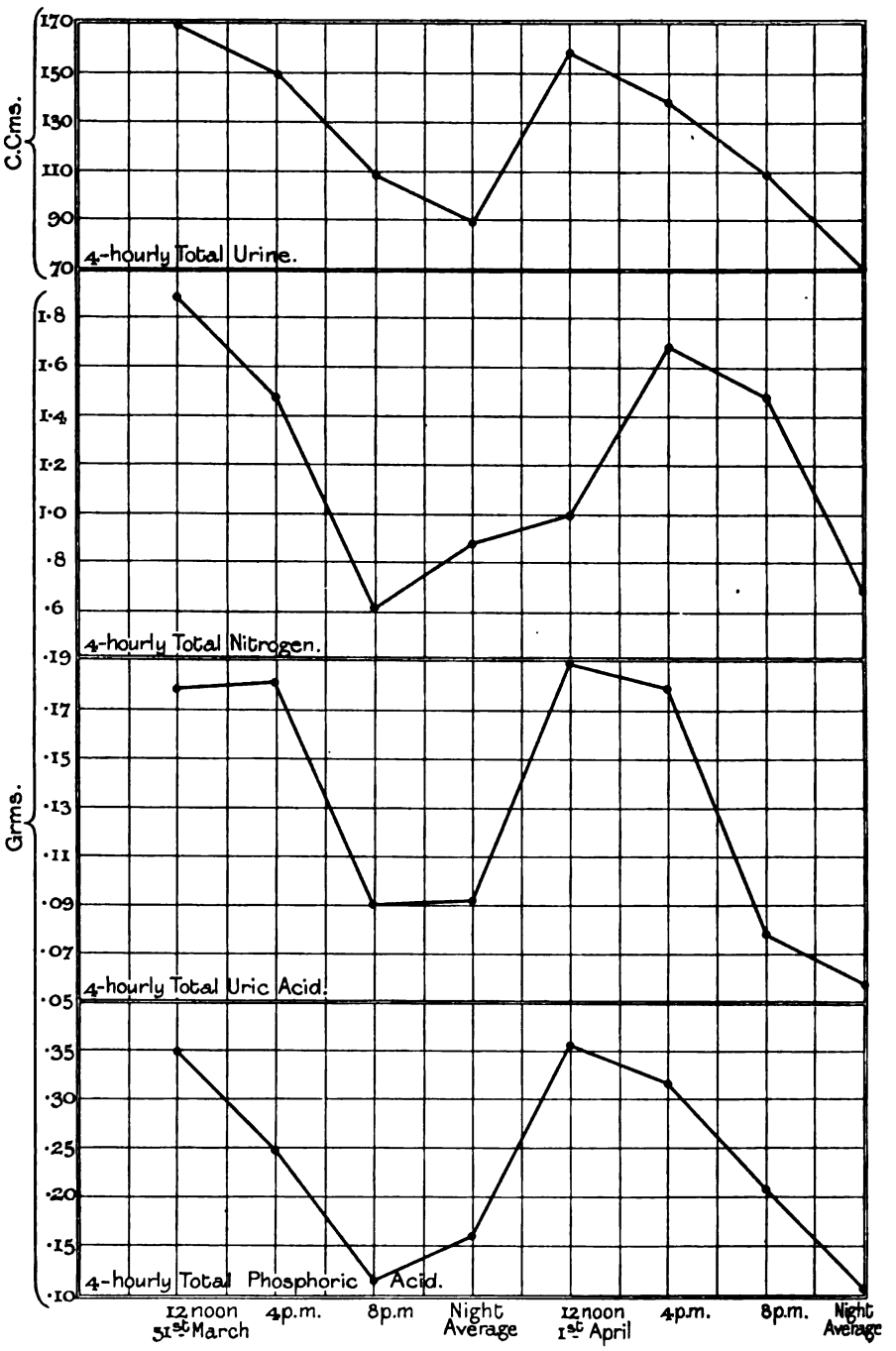
was estimated, and during March and part of April the total phosphoric acid excretion was recorded in addition.

From the tables it appears that the average uric acid output gradually rose from ·5250 gram in January to ·5991 gram in March. The average total nitrogen also rose slightly during the same period. The nitrogen contained in the uric acid formed a considerably higher percentage of the total nitrogen in February and March than in January. In March the excretion of $P_2O_5$ was not above normal limits. Though the amounts showed slight variations, the proportion of $P_2O_5$ to the total nitrogen remained at the almost constant ratio of 1 : 5, which is the physiological figure. From the tables it will be seen that the leucocyte count oscillated greatly from day to day, but showed no tendency to progressive rise or fall. On several occasions a distinct rise in the amount of uric acid took place simultaneously with a fall in the number of white cells, but not infrequently the reverse phenomenon occurred. In fact, during the period in question it is probable that the temporary rises or falls in the total leucocyte count were not necessarily accompanied by simultaneous variations of the uric acid in the opposite direction.

By taking the averages for the different months there appears to be an undoubted rise in the uric acid output, with a corresponding diminution in the total leucocytes. It cannot, however, be demonstrated that any rise in the uric acid excretion took place as the immediate result of a temporary fall of the leucocytes, lasting perhaps one or two days. All that can be said is that during these months, while the average number of leucocytes was falling gradually in an oscillatory fashion, the average amount of uric acid also rose likewise in an oscillatory fashion. Nor can any clue as to the occurrence of leucocyte destruction be obtained from the amount of phosphoric acid excreted. This was slightly higher than the control figure, but it bore the normal proportion to the total nitrogen excreted.

In view of the large absolute amount of uric acid passed in leukæmia, an attempt was made to ascertain what relationship this increased output bore to meals. Hopkins and Hope (18) found that in healthy adults who had previously fasted the uric acid maximum occurred about three or four hours after a mixed meal, while the urea maximum generally occurred later. The increase of uric acid had also a briefer duration than that of urea. Diuresis could

TABLE III.—*Urinary estimations of March 31st and April 1st, taken four-hourly.*



not account for the early excretion of uric acid after a meal, as the rise occurred in spite of great variations in the quantity of urine excreted hour by hour. Further, they showed that digestive leucocytosis might occur after a nitrogen-free meal without any associated rise of uric acid. Egg-white diet had very little influence on the output of uric acid, thus differing markedly from thymus-diet or ordinary muscle-diet. They suggest that, of the total quantity of uric acid normally excreted, that portion which bears a more immediate relation to food does not arise from nucleins but from some more soluble constituent of the diet, acting either as a direct precursor or as a factor in a synthetic process.

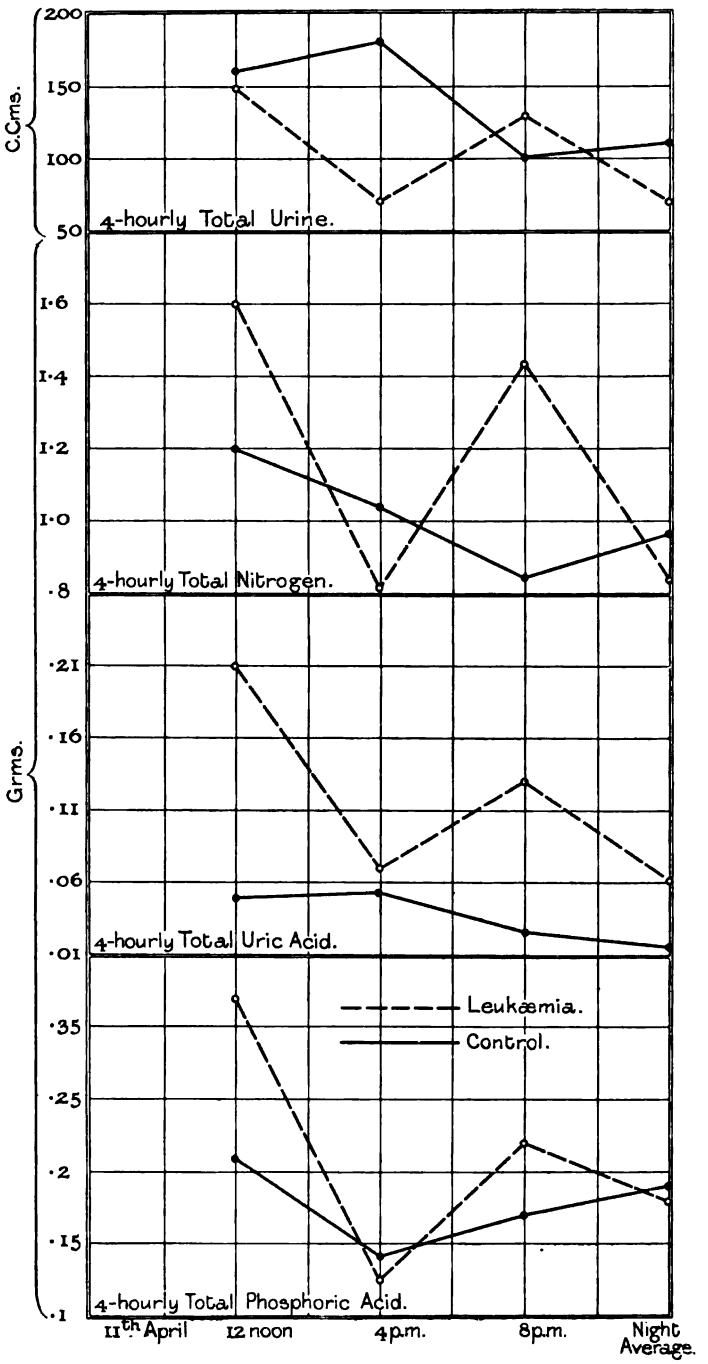
On March 31st, April 1st, and April 11th, urinary analyses were made four-hourly throughout the day, but for obvious reasons the ordinary meal-times were adhered to.

Breakfast at 7 a.m. consisted of porridge, 8 oz.; milk, 5 oz.; bread, 2 oz. Dinner at 11.30 a.m. consisted of soup, 5 oz.; bread, 2 oz.; mince and potatoes, 6 oz.; pudding, 6 oz. Tea at 3.30 p.m. consisted of milk, 12 oz.; bread and butter, 4 oz., and one egg. Supper at 7 p.m. consisted of milk, 10 oz., and bread, 3 oz.

The samples for analysis were taken at 8 a.m., 12 noon, 4 p.m., and 8 p.m., the sample at 8 a.m. being drawn from the night urine, 8 p.m. to 8 a.m. The annexed curves (*vide* Table III) of the total urine, total uric acid, total nitrogen, and total $P_2O_5$ on March 31st and April 1st show that the uric acid is invariably highest during the period 8 a.m. to 12 noon. During 12 noon to 4 p.m., an equal or sometimes slightly greater amount of uric acid is passed, after which a marked fall takes place. The total nitrogen followed a similar curve on the whole, but appeared to reach its maximum somewhat later, especially on April 1st. The phosphoric acid curve followed almost exactly the total urine curve.

On April 11th (*vide* Table IV), similar estimations were made both on the leukæmic patient and on a control patient of the same age receiving the same diet. On this day the total urine, total uric acid, and total nitrogen of the leukæmic patient followed almost exactly similar curves. Thus in each case there were two maxima occurring between 8 a.m. and 12 noon and between 4 p.m. and 8 p.m. In the control the total nitrogen

TABLE IV.—*Urinary estimations of leukæmic and control patients on April 11th, taken four-hourly.*



and total uric acid curves are quite typical, the maximum amounts being passed after breakfast and the midday meal—*i. e.* between 8 a.m. and 4 p.m.

The phosphoric acid curve also follows the total urine curve in the leukæmic patient, but in the control there is no such correspondence. After a marked fall between 12 noon and 4 p.m. there is an equally pronounced rise, which continues till 8 a.m. the following morning. The very striking differences between the absolute amounts of uric acid passed by the leukæmic patient and the control will be apparent from the table. The leukæmic curve never even cuts the control curve throughout.

It would seem, then, that, like healthy persons, leukæmic patients react to a meal by an increased output of uric acid occurring during the succeeding three or four hours, and, further, that a second maximum may take place as the result of a second meal taken four hours after the first.

TABLE V.

| Date. | Total daily urine. | Specific gravity. | Total nitrogen. | Total uric acid. | Percentage of uric acid nitrogen in total nitrogen. | Total $P_2O_5$. | Ratio of $P_2O_5$ to total N. | White cells in 1 c.mm. |
|---|---|---|---|---|---|---|---|---|
| 1904 June 12 | 650 | 1024 | 8·372 | ·3848 | 1·6 | 1·859 | 1 : 4·5 | 44,000 |
| „ 13 | 700 | 1026 | 9·408 | ·805 | 2·8 | 1·568 | 1 : 6 | 39,000 |
| „ 14 | 670 | 1021 | 7·1288 | ·6907 | 3·2 | 1·608 | 1 : 4·4 | 37,800 |
| „ 15 | 650 | 1026 | 7·644 | ·8534 | 3·7 | 1·885 | 1 : 4 | 36,000 |
| Average | 667 | 1024 | 8·1382 | ·6845 | 2·8 | 1·73 | 1 : 4·7 | |

In Table V are recorded the results of complete urinary analyses on successive days during the period when the leucocytes were progressively sinking under the influence of the X rays.

From this table it will be seen, in the first place, that the total amount of urine passed per day has slightly increased. The amounts of total nitrogen and uric acid are both relatively high,

but the percentage of uric acid nitrogen in the total nitrogen remains only slightly affected. The phosphoric acid output is also relatively high, but its proportion to the total nitrogen remains as before. It may therefore be said that with a falling leucocyte count no evidence is obtained from the urinary analyses of any great destruction of nuclein-containing tissue, and it may be assumed accordingly that the fall in the leucocytes due to X-ray influence was not a consequence of leucocyte destruction, but more probably of diminished production. The uric acid, though it has increased absolutely to a slight degree, possesses a nitrogen content which bears practically the same relationship to the total nitrogen as before, and the same may be said with regard to the phosphoric acid output.

During the last few months brief reports of urinary analyses in the course of X-ray treatment of leukæmia have appeared.

Rosenberger (19) found a diminution of the uric acid in two cases while the leucocytes were falling. After the cessation of the X-ray treatment, when leucocytes were again on the upgrade, the uric acid showed a tendency to rise.

Schleip and Hildebrandt (20) found no increase in the consumption of nitrogen. The variations in the amount of uric acid and purins were so great that no conclusions could be drawn. There was certainly an absolute increase above normal, but no special increase at the period of diminution of the leucocytes. Strümpell (21) and Joachim and Kurpjuweit (*loc. cit.*) are the only observers who found an increase of uric acid during a fall of the leucocytes.

Lossen and Morawitz (22) gave a very complete account of chemical and histological investigations in leukæmia under X-ray treatment. During the fall of the leucocytes they found a diminution in the amount of uric acid, which, however, did not run quite parallel with the fall. They attributed the fall of the leucocytes to diminished production in the blood-building organs. In another patient, who was throughout the treatment in a very exhausted condition, and who ultimately died, they found a rise in the uric acid immediately after the beginning of the X rays, and a second maximum several days after their suspension and corresponding in time to the fall of the leucocytes. In spite of extreme leucopenia the uric acid remained high. In this case, however, it is important to observe that the general condition of

the patient did not improve during the treatment, and though the total leucocytes fell markedly to subnormal limits, qualitative changes were not evident.

In a recent paper on purin-metabolism in man, Bloch (23) has recorded a few urinary analyses on an individual suffering from chronic eczema whom he exposed to the X-rays. During the exposures the leucocytes fell slightly, and there was quite an appreciable rise both of the uric and phosphoric acid.

As this, so far, appears to be the only experiment recorded in this connection, it will be advisable to await further confirmation before commenting on this interesting result.

## Part III.—Post-mortem and Histological Findings.

I append here a very brief abstract from the protocol:

General nourishment fair. Well-marked œdema of lower extremities. Musculi papillares of heart presented fatty changes.

*Lungs.*—Left bronchial mucosa red and congested.

Œdema of upper lobe. Bronchial glands on both sides slightly enlarged, the largest reaching the size of a hazel-nut. On section they presented a deep pink homogeneous-looking surface.

At the base of right lung were some old fibrous adhesions. Marked catarrh of bronchial mucosa. In lower lobe were small patches of catarrhal pneumonia.

*Abdomen.*—Mesenteric glands all distinctly enlarged, varying in size from a pea to a large bean.

*Liver* weighed 7½ lb. Consistence firm. Capsule smooth and glistening. On section the lobules were seen to be very sharply demarcated.

*Left kidney.*—Capsule stripped off easily. Cortex more voluminous than normal, and had a somewhat dappled appearance. Kidney substance somewhat anæmic.

*Right kidney* presented a similar condition.

*Pancreas* and *suprarenals* appeared normal.

*Spleen* weighed 7½ lb. Its upper and outer surface was firmly bound to the under surface of the diaphragm. The cardiac end of stomach was also adherent at its upper and inner aspect. There was a large bunch of glands at the hilus, the biggest being of the size of a bean. The organ had an extremely firm and almost fibrous consistence, and on section

had a bright red cut surface. No Malpighians could be seen. Several small recent infarctions were present along with cicatrised remains of older ones.

The lymphatic glands on each side of the spine, both in the abdomen and thorax, were considerably enlarged, and varied in size from a pea to a large bean. On section they had a pale pink, granular appearance.

Just below the diaphragm there was an enlarged gland about the size of a hazel-nut, which contained numerous small hæmorrhagic areas.

*Bone-marrow.*—The bone-marrow as seen in the sternum, vertebræ, and ribs had a pale pink colour.

### *Histological examination.*

*Spleen.*—Paraffin sections were stained by van Gieson's picro-fuchsin-hæmatoxylin, Unna-Pappenheim's methyl-green-pyronin, and Giemsa's azur-eosin.

With van Gieson's stain one is immediately struck by the development of coarse connective-tissue fibres pervading the whole pulp substance. By comparison, however, with spleen specimens from other chronic cases of leukæmia, one must admit that the fibrotic process had not advanced very far. It had, however, gone far enough to explain the failure of the X rays to reduce the splenic volume to any marked extent.

The Malpighian bodies are practically absent. Only here and there, in the neighbourhood of a large vessel running in the coarse trabeculæ, one sees small columns or groups of round lymphoid cells. Congestion of the spleen-pulp with red blood-cells is a marked feature.

The nature of the cellular constituents of the spleen-pulp demands a detailed description.

*Giemsa's azur-eosin.*—(1) Large mononuclear cells of round or oval contour with slightly vesicular nuclei and an abundant zone of intensely basophile cytoplasm form the great majority of the cells of the spleen-pulp. These cells are generally arranged in irregular clumps lying in close apposition to each other as if active division were going on. Numerous mitotic figures in all stages are seen in these cells. In the neighbourhood of the larger trabeculæ these basophile cells are specially numerous,

and along with them are groups of plasma-cells. With the Unna-Pappenheim stain the plasma-cells are readily distinguished from the basophile cells by their deep red cytoplasm, while that of the basophile cells takes on a faint pinkish tinge.

(2) Cells of the neutrophile series, whether of the polynuclear or myelocyte type, are very scarce, but here and there small numbers of eosinophilic myelocytes are seen.

(3) Small lymphoid cells occur very sparsely in comparison with the basophile cells.

(4) A few megakaryocytes with irregular pyknotic nuclei are observed.

*Lymph-gland.*—The section of a lymph-gland from the mediastinum presents a remarkable appearance. There are no lymphoid nodes to be seen, and only here and there one notes small collections of lymphoid cells in the neighbourhood of a vessel-sheath. The gland pulp has a very open character, with a fine reticular stroma.

The cell constituents are as follows:

(1) Large basophile cells, closely huddled together in rows and groups, and exactly resembling those met with in the spleen pulp. Mitoses are here also frequent. These cells, with the giant cells to be mentioned below, form a most striking picture.

(2) Giant cells appear in every field, there being often as many as eight or ten in one field of the oil immersion (Leitz $\frac{1}{12}$, oc. 4). Some of these giant-cells which lie in close apposition to the basophile cells have single large nuclei, while others possess two equal and regular nuclei. Transition forms between the basophile cells and these giant types are readily met with. Besides these there are still larger giant cells with mulberry-shaped conglomerate nuclei. The cytoplasm of these cells is faintly acidophile in the smaller varieties but strongly so in the larger forms.

Another quite distinct type of giant cell is frequent. Its nucleus may take the most bizarre form, and presents marked pyknosis. The cytoplasm has a homogeneous hyaline appearance and is strongly acidophile. It is evidently identical with the megakaryocyte of the spleen-pulp.

(3) Polynuclear neutrophile cells are fairly numerous, and a few eosinophilic myelocytes are seen.

(4) Nucleated red cells are scarce.

(5) Here and there one sees small groups of cells with ill-defined contour. They contain in their interior two or three intensely stained half-moon-shaped bodies, and the protoplasm is strongly acidophile. It is probable that these cells represent degenerated megakaryocytes, but it is difficult to explain how the broken-down nuclei should assume such regular semicircular forms.

*Marrow* (*from sternum*).—The marrow from the sternum exhibits marked hypoplasia. Bony lamellæ and strands of connective tissue traverse the section, leaving small cellular areas, which contain the following cell types:

(1) Small lymphocytes are the most numerous.

(2) Large lymphocytes and large mononuclears are also frequent.

(3) The large basophile cells, similar to those met with in the glands and spleen, are not numerous, but occur here, as elsewhere, in small clumps.

(4) Giant cells are much less numerous than in the lymph-glands. The great majority possess nuclei of the pyknotic type, with abundant acidophile cytoplasm.

(5) Collections of these peculiar cells with semilunar fragmented nuclei are also frequent.

(6) Nucleated red cells are very scarce.

*Liver.*—The liver presents the usual appearance met with in spleno-medullary leukæmia. The intracinar capillaries are quite stuffed with leucocytes, the great majority of which consist of the large basophile cells met with in the spleen and glands.

*Kidneys.*—These presented nothing remarkable.

To sum up the histological features, one may say that, so far as the glands and spleen are concerned, the normal lymphoid tissue has been replaced in both cases by large cells with strongly basophile protoplasm, and which in other respects resemble the myelocyte in morphology. In all probability these cells are identical with the basophile myelocytes of Dominici, or undifferentiated cells. The fact that mitoses are so numerous in these cells would show that active proliferation was going on. In the lymph-glands, again, the large numbers of giant cells would indicate that these had also undergone a myeloid transformation.

From the appearance of the marrow, its function as a

furnisher of neutrophile cells and red cells must be considerably curtailed.

Can we bring these changes into line with those met with in the hæmopoietic organs of experimental animals as recorded by Heineke (*loc. cit.*) and Mosse and Milchner (*loc. cit.*)?

The absence of Malpighian follicles in the spleen is a common feature in chronic spleno-medullary leukæmia, and hence cannot be regarded *per se* as the result of radiotherapy.

Nor is there any sign of active destruction of follicles having taken place by the presence of necrotic patches containing epithelioid cells and phagocyte elements. The great scarcity of lymphoid elements in the spleen-pulp is certainly a conspicuous feature, but the most remarkable change is the substitution in the spleen-pulp of proliferating undifferentiated basophile myelocytes in place of the fully-formed granular elements which one usually finds in the spleen of chronic myelogenic leukæmia. In cases of acute leukæmia these undifferentiated cells have been found in active proliferation in the bone-marrow, spleen, and lymph-glands (Aubertin [24]), and one might presume that the real cause of death was an attack of acute leukæmia superposed on the chronic form during the leucopenic stage that prevailed in the last two months. It seems to me, however, that the condition permits of another explanation in the light of Heineke's and Mosse and Milchner's experiments.

Before the commencement of the X-ray treatment one must presume that the hæmopoietic organs were already profoundly altered, and that the spleen in particular had undergone a myeloid transformation. The first result one would expect would be a great diminution in the non-granular cells of the circulating blood, as these appear to be the most susceptible to the rays. During the first series of *séances* this is what happened. After the suspension in August the lymphocyte percentage again moulded upward, while the total neutrophile percentage fell. On the resumption of the X-ray sittings, there was a further fall in the lymphocyte percentage, while the neutrophile rose.

Now, everything points to the fact that the spleen and lymph-glands were the hæmopoietic organs which were most actively functionating. Accordingly, with the ever-increasing tendency to diminished production of leucocytes imposed by the X-rays

during the second series, there now came into more prominence the Mosse and Milchner effect on the production and development of the granular cells, and hence one would expect that the polynuclears, or fully-formed varieties, would relatively diminish, while the unripe forms would increase. In short, with a normal total leucocyte count and the tendency to diminished production still present, the myeloid function of the spleen, or its power of manufacturing and sending forth into the circulation more or less fully formed neutrophile cells, must be considerably curtailed, and, moreover, the Mosse and Milchner effect must show itself by inhibiting the development of granular cells. Hence the presence in such numbers of these basophile indifferent cells, accompanied by a diminution of the fully-formed polynuclear cells of the circulating blood, might not be so unexpected a phenomenon. Whether such a spleen would serve the organism more beneficially than a more fully developed myeloid organ is difficult to decide. Most probably it would not, as undoubtedly the needs of the organism would be better served by an organ whose power of manufacturing and throwing into the circulation an excess of fully developed neutrophile cells was well maintained. The above considerations lead me to think that in the interests of the patient it would be advisable to exercise the greatest caution in continuing X-ray treatment once the total leucocyte count has reached the normal, and all the more necessary when one remembers the startling results of some of Halber and Linser's experiments. Indeed, in the very few cases of leukæmia in which fatal results have ensued in the course of X-ray treatment dangers from leucotoxic products or liberated ferments have sometimes been assigned as the exciting causes of death.

I may here refer to the fatal case recorded by Lossen and Morawitz (*loc. cit.*), who describe the histological features of the organs. So far their case is the only one in the literature which has been accurately examined in this connection. A case examined by Ziegler was shortly recorded by Krause, who mentions that it was impossible to demonstrate any changes that were not usually got in leukæmia. Lommel (25) also examined the spleen of a case of pseudo-leukæmia which had been exposed to the X rays, and laid stress on the scarcity of lymphocytes in the organs. Briefly, the changes found by Lossen and Morawitz

were as follows: In the spleen lymphocytes were rather numerous, while myelocytes and large mononuclears were very scarce. There were no Malpighians. Some spots of necrosis were observed, along with giant cells of tubercular type. (*N.B.*, in the lungs there were signs of old tubercular lesions.) On the whole, the spleen-pulp was rather lacking in cellular elements. In the lymph-glands there was also a great scarcity of lymphoid elements. The marrow was markedly hypoplastic, and there were few nucleated red cells in it. The authors conclude that the X rays may in certain cases give rise to an anatomically recognisable hypoplasia of the blood-forming organs.

To conclude, no satisfactory explanation has yet been given of the enormous improvement in the general condition of the patient under the X ray. It is at least difficult to bring it into line with the blood changes, unless, of course, one takes Senn's view, that the rays destroy or inhibit the development of the hypothetical parasitic agent in leukæmia.

Certain investigations (elsewhere recorded) which I have made on the *rôle* played by the leucocytes of spleno-medullary leukæmia in the process of phagocytosis of bacteria have shown that in the leukæmic serum the substance preparing the bacteria for ingestion by the phagocyte is in normal amount (opsonin of Wright), as measured by normal leucocytes, while a very much lower index is obtained when measured by the patient's own leucocytes. The myelocytes have exceedingly feeble phagocytic power, and hence any factor that increases the number of ripe polynuclears in the circulating blood must also render the normal supply of opsonin available for purposes of efficient phagocytosis, and hence of the most efficient removal of effete matter from the tissues. Probably in some such way as this the general improvement in the well-being of the patient under X-ray treatment is brought about.

To Dr. Bulloch I am greatly indebted for assistance in the preparation of the charts.

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## 9. *The mammary glands and the fœtus.*

By S. G. Shattock.

### *De ratione mammam inter et fetum.*

Summarium.

Nuper monstrabat Starling[1] extractum telarum diversarum ex cuniculorum fetubus mammam incitare cuniculi virginis augescere.

Injectum est extractum quotidie sub cutem aut in cavum abdominale per dies plurimas.

Nullum secernitur lac, tamen, glandulâ augescente.

Hæc me inducunt experimenta quædam narrare anno 1901 confecta.

[1] "Croonian Lectures," Royal College of Physicians, London ('Lancet,' August 26th, 1905).

Generantne mammæ augescentes per gestationem normalem secretionem aliquam internam quæ ad fetum augescendum necessaria sit?

Caviarum mammis excisis, postquam partes sanatæ sunt animalia cum maribus congregata sunt.

Gestaverunt caviæ atque partæ sunt, catulis ad normam evolutis.

Ex his experimentis videtur mammas nullam secretionem internam ad fetum augescendum necessariam per gestationem generare.

The recent work of Professor Starling on the action of extracts of fœtal tissues upon the mammary glands leads me to record some experiments of a converse nature which I carried out five years ago, but which, owing to their results having been negative, have not hitherto been published.

Professor Starling's work was made known in the Croonian Lectures delivered at the Royal College of Physicians ('Lancet,' August 5th, 12th, 19th, and 26th, 1905), the particular lecture in which it is given being the fourth.

The tissue used was pounded for one hour with sand, so as to break up the cells, and after the addition of a little salt solution, mixed with Kieselguhr; the resultant powder, which was almost dry, was then subjected in a Buchner's press to a pressure of 300 atmospheres. The whole of the fluid of the tissues containing their soluble constituents was pressed out, and the fluid was afterwards sterilised by passage through a Berkefeld filter into a sterilised flask. The extracts used were of the viscera of rabbit fœtuses and of the bodies of the fœtuses themselves. The injections were made subcutaneously and intra-peritoneally.

The result of the injections, when made into the virgin rabbit for prolonged periods, is to produce hyperplasia of the mammary glands, beginning, as in normal pregnancy, with proliferation of ducts, and later on leading to the formation of secreting alveoli. No milk could be obtained from the nipple on squeezing, but only a watery fluid. The extracts could be boiled and filtered through a Berkefeld candle without being rendered inefficacious,

and were thus proved to contain a thermostable substance not to be included in the class of ferments. Professor Starling's conclusion from these experiments was that the fœtus during its growth furnished an internal secretion which reached the maternal circulation and incited the growth of the mammary glands by a direct biochemical action. For substances of this nature, and producing similar direct results, he has proposed the name "hormones" (chemical "messengers").

The result might be compared with the direct stimulation of the pancreatic secretion which is brought about by the formation and absorption of secretin in the intestinal epithelium; or, better, seeing that there is an overgrowth of tissue, and not merely increased activity of secretion, with the overgrowth of hair in certain regions of the body, which occurs in both sexes at puberty, and which may be attributed to the formation of an internal secretion by the testicle or ovary, seeing that the removal of these glands before puberty is followed by an absence of such overgrowth in the same positions.

The evolution of the mammary glands, however, does not proceed, under these experimental conditions, to the stage of lactation. There results a building up of the gland—proliferation of its cells and the formation of new secreting alveoli; the katabolism of the cells, with the accompanying formation of milk, occurs only with parturition—*i. e.* when the source of the anabolic stimulus is removed.

The question I had put to myself was, Do the enlarging breasts of pregnancy furnish an internal secretion which is necessary for the growth of the fœtus?

In November, 1900, the mammary glands were experimentally removed in a series of adult guinea-pigs. A T-shaped incision was made through the skin of the lower part of the abdomen, each of its arms passing a short way above each nipple. The fat and mammary tissue imbedded in it were easily turned off with the fingers and forceps from the surface of the abdominal muscles; the ducts were cut across close to the under side of the nipple. After the mammary gland and pertaining fat had been removed the fat below the pubes was picked away so as to expose the crura of the clitoris. The wound was washed out with 1 : 20 carbolic acid and united by continuous suture, strips of gauze being finally laid over the incision and painted with

collodion. The animals were placed on cotton-wool, which was daily renewed, and afterwards on sawdust. On examining the seat of operation fourteen days later, it presented in each animal a long transverse ulcer, the edges of the flaps evidently having sloughed. Seven weeks after the operation the wound had in three of the animals soundly healed. The abdomen in each being quite flaccid and presenting only a narrow scar, and the guinea-pigs being in good health, a male was put to each in February, 1901. One became pregnant; it was parted from the male, and on May 2nd bore three young; two of these were of full size, one was below it. Of the two larger one was artificially fed with cow's milk syphoned through a thread of worsted, which it at once learned to use. It lived six days; when dead its weight was 56 grams.

From this result the conclusion to be drawn is that the mammary glands during pregnancy do not furnish an internal secretion which is necessary for the proper development and growth of the fœtus.

*December 19th*, 1905.

*P.S.*—After the foregoing paper was read Dr. Richard Raikes, of Midland, Ontario, who happened to see a note of it in the 'New York Medical Record,' was good enough to communicate to me the following case: In August, 1904, Dr. Raikes attended a lady in her first confinement and delivered her of a healthy female child, although both her mammæ had been removed two years previously for malignant disease. The child is at present living and well.

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## 10. *Primary tuberculosis of thyroid.*

By H. A. Lediard.

The specimen came from a strong, healthy-looking country labourer, aged 21 years, who lived at Aspatria, a goitre district in Cumberland.

There was a moderate-sized enlargement of the left lobe of the thyroid gland, which caused neither pain nor pressure on the trachea. There was nothing unusual felt or seen, but the elasticity of the "tumour" was clearly due to fluid in a cyst.

After removal the "tumour" was found to be of the size of a small orange, and on section an ounce or more of sero-purulent fluid escaped from a cavity in its centre.

Microscopic sections made through the thyroid from the capsule down to the cavity show the lesion to be tubercular. The wall of the cavity is very thick and is composed of typical granulation tissue. Immediately outside this granulation layer there is a good deal of fibrous and cellular overgrowth of the thyroid stroma which is seen radiating throughout the gland. There are numerous giant-celled systems seen in the stroma, some massed together, forming larger cellular areas. A few are also seen situated in the granulation-tissue of the wall of the cavity. (The systems do not originate in the follicular epithelium, but are situated in the connective tissue.) Tubercle bacilli were not found in any of the sections.

Cultures were attempted from the contents of the cavity found in the gland, but they remained perfectly sterile, so that the abscess cavity was not of a septic nature, and no pyogenic organisms were found in the contents on microscopical examination, thus confirming the negative results given by the cultures.

In spite of the non-discovery of tubercle bacilli, the histological appearance is typical of tubercular disease, and there can be no question as to the nature of the condition.

Tubercular infection of the thyroid gland is of very rare occurrence even in general tuberculosis; and in cases of widely-spread tubercular disease of the lymphatic glands of the neck, where the thyroid is simply imbedded in the mass, the thyroid itself has been found free from infection.

In the case related there was no discoverable source of tubercular infection, either prior or subsequently to operation. The wound healed at once, like any other thyroidectomy, and the patient has remained well and strong in all respects.

Many cases of tuberculosis of the thyroid are on record in the 'Transactions,' but in all the thyroid merely shared in a general tuberculosis. In the present example the disease is not secondary to any discoverable lesion elsewhere, and the case appears to be one of primary infection, which in its development resembled an ordinary thyroid enlargement, and was operated upon in ignorance of its real nature.

*October 17th*, 1905.

11. *An investigation on phagocytosis, dealing particularly with the cells concerned during the first twenty-four hours after the intra-peritoneal introduction of bacteria, chalk, nucleic acid, pyotoxins, etc., and the changes found in the blood and bone-marrow.*

By Leonard S. Dudgeon and Athole Ross.

(With Plate II.)

*De cellulis phagocytis ut indagatis per horas viginti quattuor postquam in cavum abdominale injectæ sunt bacillorum culturæ aut cretæ pulvis, etc., unâ cum effectibus in sanguine et in ossium medullâ concurrentibus.*

(Cum tabulâ II.)

Summarium.

In hoc opusculo describimus quomodo afficiuntur sanguis, ossium medulla, omentum, atque exudatio intra-peritonealis postquam in cavum abdominale injectæ sunt culturæ aut *Staphylococci pyogenis aurei* aut *Staphylococci pyogenis albi* aut *Streptococci pyogenis* aut *Pneumococci* aut *Bacilli pyocyanei* aut acidum nucleicum aut liquor sodii chloridi (75 per cent.), aut creta, deinde, minutissime divisa ac in liquore sodii chloridi (75 per cent.) suspensa.

Animalia quibus usi sumus cuniculi et caviæ fuerunt.

Experimentis factis, ex animalibus quædam interfecta sunt post partem horæ quartam, quædam post horam unam, post horas duas, post horas quattuor, post horas octo, quædam atque post horas viginti quattuor.

Examinatus est sanguis in singulis animalibus et antequam et postquam culturæ injectæ erant, observationibus in tabulis deinde expositis.

Numerati sunt leucocyti in preparationibus microscopicis sanguinis, ossium medullæ, et exudationis intraperitonealis.

In pluribus exemplis cellulas super omentum phagocytos esse invenimus etsi exudatio ipsa in cavo abdominali sterilis esset.

Ex omento *Staphylococcus pyogenes albus* cultus est postquam injecta erat creta in liquore sodii chloridi (75 per cent.) suspensa.

Experimenta omnia secundum artem bacteriologicam confecta sunt.

Per partem horæ quartam post experimentum, cellulæ sanguinis polymorphonucleatæ cum granulis minutis, sive neutrophilæ, multiplicabantur; cellula in exudatione intraperitoneali præcipua aut lymphocytus parvus erat aut cellula polymorphonucleata cum granulis crassis, sive eosinophila. Post partem horæ quartam cellulæ polymorphonucleatæ neutrophilæ in exudatione dominatæ sunt.

E cellulis phagocytis cellula polymorphonucleata eosinophila princeps erat per partem horæ quartam, per horam primam, et per horam secundam; cellula deinde polymorphonucleata neutrophila.

Harum cellularum genera omnia præter lymphocytos parvos atque cellulas polymorphonucleatas eosinophilas agglutinabantur.

De ossium medullâ, post partem horæ quartam cellula quæ per horas viginti quattuor præcipue multiplicabatur, illa fuit generis lymphoidis.

Erythrocyti nucleati præcipue multiplicabantur postquam aut *Pneumococcus* aut *Streptococcus pyogenes* in cavum abdominale injectus fuisset. Medulla lymphoerythroblastica fit.

Non apparet phagocytosis, nec cernuntur figuræ mitoticæ in medullæ cellulis.

Cellulæ multinucleatæ, sive myeloides, in hâc reactione implicari non videntur.

### *Introduction.*

Although so much valuable work has been done on the subject of phagocytosis by various investigators, of whom we may especially mention Metschnikoff, Leishmann, Herbert Durham, Isaeff, Robert Muir, and A. E. Wright, very little advance has been made as to the character of the cells which appear in the blood, bone-marrow, peritoneal fluid, and on the surface of the great omentum during the earliest stages of inflammatory processes.

We have endeavoured in these experiments on phagocytosis to show how the various parts of the body already referred to react to certain bacterial and non-bacterial substances within the first thirty hours from the time of inoculation. In every instance the injections were made intra-peritoneally into either guinea-pigs or rabbits. Special intervals of time were employed in all our experiments, which were similar in almost every instance. The body fluids and tissues of every animal were examined at intervals of a quarter of an hour, one hour, two hours, four hours, six or eight hours, and at longer intervals of seventeen to twenty-four hours respectively after inoculation. Those micro-organisms were used which are known to be the most important agents in the bacteriology of peritonitis.

We have recorded our results as fully as possible, and have taken every precaution to avoid the common errors which are liable to arise owing to lack of control experiments and through placing too much reliance on solitary observations.

In this research we have enumerated cells in the peritoneal exudate which appear to be phagocytic, but we have not counted the number of organisms in each cell. Owing to the extreme difficulty of accurately determining whether an organism is in a cell or on the surface, we are fully alive to the fact that the numbers given in our tables cannot be strictly accurate, and it is for this reason that we have not determined the number of

organisms or particles of foreign matter in each phagocyte. We have corrected this error to some extent by always counting a large number of cells (400 to 500), but even allowing for this fact, such experiments are always open to criticism. In conclusion, we may add that we seldom found more than five or six micro-organisms per cell, and if the numbers much exceed this limit an accurate estimation is an absolute impossibility.

### *Technique.*

One of the most important objects in this research on phagocytosis was to determine, as fully as possible, what changes occurred in the cells of the blood, peritoneal fluid, omentum, and bone-marrow after certain bacteria, their toxins, and various fluids had been injected into the peritoneal cavity, and also to make a study of these changes at definite intervals.

In each set of experiments on a given micro-organism or other substance six guinea-pigs were inoculated intra-peritoneally and afterwards killed for examination in the following order:

The first animal at the end of fifteen minutes.
The second „ „ „ one hour.
The third „ „ „ two hours.
The fourth „ „ „ four hours.
The fifth „ „ „ six hours.
The sixth „ „ „ twenty-four hours.

In the case of the *pneumococcus* and of the *Streptococcus pyogenes* rabbits were used, the same intervals of time being observed. In a few instances for some special reason other times were adopted for these experiments.

### *Bacteriological technique.*

The following micro-organisms were used in this research (we especially selected those bacteria, as already stated, which are known to be the most important agents in the bacteriology of peritonitis):

(1) The *Staphylococcus pyogenes aureus,* isolated from a case of acute infective bone disease.

(2) The *Staphylococcus albus,* from a case of acute peritonitis.

(3) The *Streptococcus pyogenes,* from a case of acute peritonitis.

(4) The *Pneumococcus*, from a case of acute peritonitis.

(5) The *Bacillus pyocyaneus*, from a case of acute peritonitis.

(6) The *Bacillus typhosus*, from a case of typhoid fever (spleen).

(7) The *Bacillus coli*, from a case of acute peritonitis.

(8) A hypodermic injection of $\frac{1}{15}$th of a grain of morphia was given to each animal before it was inoculated with the colon bacillus.

(9) A strain of the *Bacillus coli* killed by exposure to heat (twenty minutes at 60° C.).

(10) The *Bacillus aerogenes capsulatus*, isolated from a case of acute emphysematous gangrene.

(11) Filtered cultures of the *Bacillus pyocyaneus* (comprising three strains), isolated from cases of acute peritonitis.

In all cases twenty-four-hour broth cultures were employed, with the exception of the *Bacillus aerogenes capsulatus*, which was grown anaerobically on agar for four days at 37° C.

A series of experiments on similar lines was made with each of the following substances:

(1) A 2 per cent. solution of nucleic acid.

(2) Sterile normal saline solution (0·85 per cent.).

(3) A suspension of finely divided chalk in normal saline which was carefully sterilised previous to use.

The inoculations were performed with sterilised glass hypodermic syringes, and were made in every instance intra-peritoneally, as follows: At the site of the inoculation the hair was carefully removed, the skin was next treated with ether soap followed by ether, and then the needle was introduced in the usual way.

A *dose* of $\frac{1}{4}$ to $1\frac{1}{2}$ c.c. of a bouillon culture of the various micro-organisms was injected into the peritoneal cavity. The same dose of solutions containing the other substances already referred to was also employed. An exception to this occurred in the case of the *Bacillus pyocyaneus*; the various strains used were found to be so highly virulent that only a few minims could be safely injected without grave risk of the pig dying before the time limit in the longer experiments was reached. Also, only $\frac{1}{4}$ c.c. of an agar emulsion of the *Bacillus aerogenes capsulatus* was employed.

In all cases immediately after the animal had been killed

under chloroform a systematic examination of the peritoneum and great omentum was made, the results of which were recorded, with a note as to the amount of peritoneal fluid found.

### *Hæmatological technique.*

Figures have been published purporting to give a normal standard for the number of leucocytes per c.mm. and also for the percentages of the white cells in the differential counts of guinea-pigs' and rabbits' blood.

A large experience of the leucocyte counts and also of the differential counts made on guinea-pigs and rabbits in the normal state has shown that even an approximately correct standard cannot be obtained for their physiological blood.

Such statements as "the normal number of leucocytes in guinea-pigs' blood per c.mm. is 10,000," or that "the coarsely granular eosinophile cells amount to 10 per cent.," will be found to be inaccurate in the majority of cases.

To avoid so grave an error, a count of the number of leucocytes per c.mm. and a differential count of 500 white cells were obtained *in every instance* just previous to the inoculation experiment.

The method employed for the leucocyte count was that devised by Strong and Seligmann; for the differential count blood-films were taken on cover-slips in the usual manner. The blood was obtained from the animal's ear, which had been thoroughly cleansed.

The films were stained with Professor Leishman's modification of Romanowsky's stain. We used a 0·4 per cent. solution of the powder in absolute methylic alcohol (Kahlbaum).

The stain was poured on to fix the film for half a minute, double the volume of distilled water was then added for seven minutes,[1] stain and water were now removed, and distilled water in sufficient quantity to completely cover the film added for two minutes; the film was then washed by squirting on distilled water, dried between cigarette-paper, and mounted in canada balsam.

[1] It is generally considered necessary to mix the stain and water on the cover-slip, but we have found from a very wide experience that there is no advantage in doing so.

The times given are only approximate, as they vary somewhat with each freshly prepared sample of stain.

At the appointed time after the inoculation the animal was rapidly killed under chloroform, *but immediately before the chloroform was administered* a leucocyte count and film preparations of the pathological blood were taken in precisely the same manner as already given in detail for the physiological blood.

In every instance a differential count of 500 cells was done on the normal and on the pathological blood under the one twelfth oil immersion lens.

### *The peritoneal fluid.*

*Immediately* after the death of the animal "hanging drop" and film preparations of the peritoneal fluid were made.

The "hanging drop" was obtained on a sterile platinum loop, transferred to a cover-slip, mounted on a hollow-ground slide ringed with vaseline and examined at once by the one twelfth oil immersion lens.

The film preparations were made and stained in identically the same manner as in the case of the blood-films, except that the sample of the Leishman's stain which was used for this purpose was of greater dilution.

A differential count of 500 cells was also made with the one twelfth oil immersion. Smear preparations were made from the omentum and stained in the same way. The warm stage was also used to examine the phenomena of phagocytosis in hanging drop preparations.

### *The bone-marrow.*

The marrow was obtained in every case from one of the long bones. Dr. C. Price-Jones' method of making film preparations of the bone-marrow was at first tried, but without the success which Dr. Jones has claimed for it.

A special method of making a streak-film preparation was accordingly substituted. The technique was as follows:

Two clean slides, A and B, were prepared. On to the upper

end of A a drop of marrow was placed; this was next gently smoothed out by rubbing it with the end of slide B.

This slide was now inclined at a angle of 45° to A and the marrow quickly, but *gently*, streaked out along the whole of the surface of slide A. The slide B was then discarded.

The most important part of this manipulation consisted *in exerting no more pressure with B on A than was necessary to keep their surfaces in smooth and continuous contact while making the streak.*

If the preparation is satisfactory a thin, even film will result.

To prepare the film for staining a portion was selected and enclosed between walls formed of melted paraffin. These served to limit the action of the stain to the desired part of the film and to prevent undue and unequal staining of the whole film.

Leishman's stain was employed for these in the same way as for the blood-films. Many beautiful preparations were made by this method. All specimens of marrow were obtained *immediately after the death* of the animal under chloroform.

### *A source of error in differential counts.*

Five hundred cells were nearly always enumerated, both in the blood films and in those prepared from the peritoneal fluid, so as to eliminate as far as possible any sources of error which occur from counting an insufficient number of cells.

In the case of the marrow at least five hundred cells were counted, and in a great many instances one thousand.

Occasionally the percentages had to be worked out from smaller numbers of cells, but on the whole this was exceptional.

For obvious reasons an estimation of the number of each variety of white cell present per c.mm. of blood is given in every instance.

### *Technique of experiments on the omentum.*

A series of experiments on guinea-pigs was undertaken to determine if any micro-organism could be grown from the omentum. It has already been shown by Dudgeon and Sargent how important is the part which the *Staphylococcus albus* plays

in the bacteriology of peritonitis, and we thought that perhaps we could throw still further light on the subject if we conducted these few experiments.

The omentum was examined as follows:

(1) In the normal state.

(2) After the intra-peritoneal inoculation of sterile normal saline or a suspension of sterilised chalk in normal saline.

It is unnecessary to recapitulate the technique as regards the method of inoculation or the dose of normal saline or chalk employed.

The animals used comprised the following:

(1) A series of presumably healthy guinea-pigs (evidence of disease was sought for but not found).

(2) A second series, which had been inoculated intra-peritoneally with sterile normal saline.

The pigs of this series were killed with chloroform and examined at the following intervals:

(*a*) Two hours after inoculation.

(*b*) Four „ „ „

(*c*) Eight „ „ „

(*d*) Twenty-four hours after inoculation.

(3) An exactly similar series of pigs received an intra-peritoneal inoculation of a sterile suspension of chalk in normal saline.

The most rigid aseptic precautions were observed as to the sterilisation of instruments, the integuments of the animals, and our own hands. The following points may be especially cited:

(1) At the site of inoculation the hair was shaved over a wide area and the skin thoroughly cleansed.

(2) Immediately after death by chloroform the coat was sterilised with a hot knife from the sternum to the pelvis.

The abdominal muscles and the peritoneum received a similar sterilisation before they were incised.

(3) A fresh pair of sterile forceps and scissors were used for every pig to obtain the piece of omentum.

The omentum was transferred to a culture-tube of broth, which was then incubated for four days at 37° C. The usual bacteriological methods were next employed to determine the nature of any micro-organism found.

In all cases control tubes were put up from the saline and

chalk solutions to be used, and on no occasion was there any evidence of contamination.

In addition, cultures were taken from the peritoneal fluid (with the same precautions) into broth, but these proved to be sterile *without exception.*

### *The normal peritoneal fluid.*

Eugen Opie has stated that the peritoneal cavity of the guinea-pig contains normally a small amount of clear fluid in which are suspended a considerable number of cells.

Kanthack and Hardy, quoted by Opie, found the following varieties:

(1) Finely granular polymorphonuclear and coarsely granular polynuclear cells, forming from 30 to 50 per cent. of the total number.

(2) Basophile granulated cells in small numbers.

(3) Cells equivalent to the small lymphocytes of the blood.

(4) Large mononuclear cells with round, indented nuclei and fairly abundant non-granular protoplasm, which are the large hyaline cells or the macrophages of Metschnikoff.

Durham has maintained that the normal cells of the guinea-pig's peritoneal fluid comprise the large hyaline, the small lymphocyte, and the coarsely granular eosinophile cell, and he has called attention to the absence of the finely granular polymorphonuclear cell in this fluid.

The results which we have obtained from guinea-pigs are not in accordance with the findings of the above authors as regards the presence in large numbers of finely granular and coarsely granular polynuclear cells in the normal peritoneal fluid. We agree with the statement that the amount of fluid is usually very small, but find that the majority of the cells are of the endothelial type; these cells presented a relatively large, somewhat darkly staining nucleus, showing a coarse reticulum, while the cytoplasm stained less deeply and showed a reticulated yet not truly granular structure.

These endothelial cells numbered about 70 per cent. of the total, while over 25 per cent. of the remainder were cells which were indistinguishable from the small lymphocytes of

the blood, except that they were in many instances smaller. We have sometimes observed large hyaline cells in the fluid from the normal peritoneum, but not amounting to more than 2 per cent. of the cells present. One of us has occasionally seen a very few finely granular polmorphonuclear cells in the peritoneal fluid of presumably healthy guinea-pigs, which had been inoculated intra-peritoneally with human ascitic fluid from cases of cirrhosis of the liver (the animals being killed after surviving for many weeks). These cells were certainly very scarce, and even in the above-mentioned cases did not amount to more than three per cent. of the white cells. We are inclined to agree with Durham, who has stated that the finely granular polynuclear cells are not found in the normal peritoneal fluid of this animal.

We have never been able to demonstrate the presence of the coarsely granular polynuclear cell in the peritoneal fluid of either a normal guinea-pig, rabbit, or human subject, although Leishman's stain was used in all cases.

With the rabbit our results have been very similar to those obtained with guinea-pigs. Probably the finely granular polynuclear cell is normally absent from the peritoneal cavity of the rabbit, although it is nearly always found there in these animals in association with the almost invariable presence of the coccidium oviforme, and is the natural outcome of inflammatory reaction due to that parasite. Durham has fully noted this fact, and has pointed out that the peritoneal cavity of the rabbit is perhaps not a very suitable field for experimental research on phagocytosis.

We have examined many films made for us from the human peritoneum of cases in which abdominal exploratory operations had been performed when there was no evidence of any abnormality in the peritoneum itself.

In all such instances the histological examination of this fluid showed cells resembling those already described in the peritoneum of the guinea-pig.

In conclusion, we may add that some half-dozen normal guinea-pigs were specially examined by us with a view of determining what varieties of cells were physiologically present in this fluid.

*The great omentum.*

It is an undoubted fact that the great omentum plays a very important part in the bacteriology of peritonitis, but still more so in its relation to cellular pathology.

To Herbert Durham is due the credit of first drawing attention to these facts. It is surprising, therefore, that so little notice should have been paid to the functions of this portion of the peritoneum when we consider the importance of Dr. Durham's valuable paper.

*Bacteriology of the great omentum.*—The important part which the omentum plays in peritonitis, if we can judge from surgical text-books, has almost escaped notice.

Klein has remarked that the omentum is intensely injected in guinea-pigs dead from peritonitis, and may sometimes show petechial hæmorrhages. This condition, as Durham has already noticed, is a constant feature of peritonitis in both man and animals. In guinea-pigs dead from peritonitis we always find the omentum rolled up towards the diaphragm; this feature of the great omentum may often be observed a few hours after an intra-peritoneal injection of a pathogenic organism. The cause of this rolling up is due, as Durham has stated, to the peristaltic movements of the intestines.

The term "chemical peritonitis" introduced by Tavel and Lanz, has now been shown to be incorrect owing to the researches recently made by Dudgeon and Sargent on the bacteriology of peritonitis. These observers have shown that the so-called chemical peritonitis is really a peritonitis due to the *Staphylococcus albus*. They have also found that the *Staphylococcus albus* and other micro-organisms may be found on the surface of the omentum although the peritoneal exudate may have been sterile.

The importance of these facts is overwhelming. It proves beyond question that the omentum should be examined in every case of peritonitis and in every animal experiment, and that the examination of the peritoneal exudate alone may be of little value. Durham questioned the accuracy of the term "chemical peritonitis" in his classical monograph on peritoneal infection to which we have already referred. He states: "Pieces of omentum will sometimes show, both microscopically and in culture, that

microbes are present, whilst the fluid of the peritoneum is sterile. These remarks apply to the peritonitis of man and that produced experimentally in animals." In conclusion, Durham adds : " These facts make one chary of accepting the 'chemical (aseptic)' peritonitis of Tavel and Lanz as well authenticated in the absence of more thorough evidence."

Our own investigations on the bacteriology of the great omentum in both man and animals are of interest and are referred to elsewhere in this communication; but suffice it to state here that (1) the normal omentum is not always found to be sterile, since in large numbers of instances the white staphylococcus can be cultivated when pieces of this tissue are dropped into broth; (2) the peritoneal exudate will be found to be sterile after the injection of sterile chalk or sterile normal saline into the peritoneal cavity of animals, while the white coccus can be obtained from the omentum in many instances in the same animals whose peritoneal exudate has been found to be sterile.

In conclusion, it will be convenient here to again draw attention to one of our experiments in which we had injected the *Bacillus aerogenes capsulatus* into the peritoneal cavity of a guinea-pig.

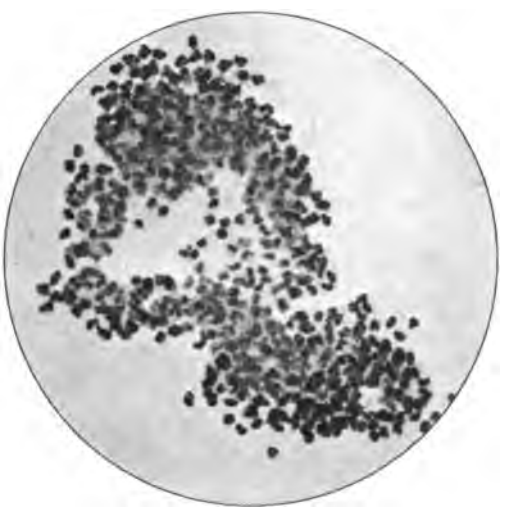
The animal was killed at the end of twenty-four hours from the time of inoculation, and film preparations were made from the peritoneal exudate and from the great omentum.

A differential count of the cells present in the peritoneal exudate showed 451, or 90·2 per cent., of finely granular polynuclear cells, *but none contained micro-organisms,* while on the great omentum 498, or 99·6 per cent., were present and *every cell was phagocytic.* This experiment and many others confirms, if it were necessary, the value of the examination of the great omentum in every case of peritonitis, as Durham originally pointed out.

*Cytology.*—The intensely active phagocytes described by Metschnikoff as the macrophages are derived from the endothelial cells of the great omentum and also from other situations. During the macrophage stage Durham has observed the large cells of the omentum to be amœboid. Foci of multinuclear and binuclear cells occur, from which cells having all the appearances of the free macrophages are budded off. The large hyaline cell met with in the blood is also of this class and many other mono-

nuclear cells. These cells Metschnikoff and others have shown to play an important part in peritonitis after the first sixteen hours. Durham has found large numbers of these cells in the great omentum englobing micro-organisms and also microphages. Numerous observers have stated that from five to six minutes, up to and including one hour, after an intra-peritoneal injection, the peritoneal fluid becomes almost cell-free. This leucopenic stage has generally been considered by Metschnikoff and others to be due to the fact that the cells are dissolved. Durham has shown, however, that the cells, which, as we know, have a strong

FIG. 24.



Showing clumping of the finely granular polynuclear cells in the peritoneal exudate of the guinea-pig after intra-peritoneal injection.

EXPLICATIO FIGURÆ.

Monstrat figura cellulas polymorphonucleatas minute granulosas, sive neutrophilas, in exudatione agglutinatas post injectionem intraperitonealem.

tendency to clump, are gathered together on the great omentum. The only cells which are found during this period in the peritoneal exudate according to these authorities are the small lymphocytes, which, as Durham has shown, do not form part of the clumps present in the peritoneal fluid during this stage, and therefore are much less readily attracted towards the great omentum.

Our results differ in many points very considerably from the observations of most of the previous workers on this subject. We have found that the mononuclear cells are generally the most numerous in the peritoneal exudate at the end of the first quarter of an hour after inoculation, but we have also noted that the fluid in the peritoneum is often abundant and the cells likewise, while in many instances cells other than the small mononuclears are plentiful in the exudate at this period.

In some cases, however, the coarsely granular eosinophile was found to be the chief cell, in other instances the large mononuclear. In every instance the clumping of the cells was obvious at this period; the clumps were both small and large, but generally small, while the lymphocytes were usually free, as Durham has shown. In one instance the peritoneal exudate of an animal was examined half an hour after inoculation, in which case the endothelial cell formed no less than 86·2 per cent. of the total, and 145 out of 500 were found to be phagocytic. It is, of course, impossible to derive any exact observations from the results of a solitary experiment. If, however, we refer to the one-hour cases we shall find that in most instances the finely granular polynuclear cell formed the chief variety of leucocyte at this stage. Durham considers that the leucopenic period actually terminates with the appearance of these cells. He adds, however, that for some time after the arrival of the microxycyte the fluid remains leucopenic. With this remark we cannot agree, as will be shown by referring to the tables which are given below.

*Peritoneal exudate examined at the end of fifteen minutes.*

| No. of observations. | Amount of peritoneal fluid. | Nature and number of cells. |
|---|---|---|
| 14 | Large amount—9 cases.<br>Fair „ —2 cases.<br>Small „ —2 cases.<br>None in one case. | Cells abundant in 9 instances, in small number in 5 cases. The small mononuclear cells amounted to over 90 per cent. in 8 examples. In the remaining instances in four examples the coarsely granular eosinophiles formed the large majority of the cells, and in two cases the endothelial cell was the most common variety. In both of the last mentioned instances the peritoneal exudate was obtained from rabbits. |

*Peritoneal exudate examined at the end of one hour.*

| Number of observations. | Amount of peritoneal fluid. | Nature and number of cells. |
|---|---|---|
| 14 | — | In 8 cases the cells were numerous, in the remaining instances scarce. In 9 examples the finely granular polynuclear cells amounted to over 50 per cent., in 1 case 97·2 per cent.; in the remaining 5 instances they were either equal to or less than one of the other varieties of leucocytes. |

*Experiments on the omentum.*

In connection with their work on the bacteriology of peritonitis, Dudgeon and Sargent have noted the fact that in every class of case the *Staphylococcus albus* is the first organism to appear in the peritoneal cavity and that organisms are frequently found on the surface of the gut, but not always in the same cases, in the exudate.

We were thus induced to undertake the following short series of experiments in the hope that they might lead to additional information as to the part played by the omentum in peritoneal phagocytosis.

A reference to the technique will amply show how every precaution was taken in procuring the specimens of omentum to avoid contamination from all possible sources.

*The first series of six guinea-pigs* were all examples of healthy animals. In three instances an abundant growth of the white coccus was obtained from the omentum, in one a slighter but quite definite growth, while the remaining two cases proved sterile.

In every animal of this series the peritoneal exudate was sterile.

*The second group of animals all* received an intra-peritoneal injection of a sterile solution of normal saline, with the result that the *Staphylococcus albus* was grown from the omentum in all three cases (after two, four, and eight hours) and again in every instance the peritoneal fluid was sterile.

*The final series of guinea-pigs* was similarly inoculated with sterilised chalk in normal saline. Here the white coccus was grown from the omentum not only after two, four, and eight hours, but also at the end of twenty-four hours (in three examples

out of four). In every instance the peritoneal exudate proved to be sterile, thus giving in this respect a uniform result throughout this research.

It is hardly necessary to add that the materials used for inoculation were proved sterile by cultural tests.

The conclusions warranted by these experiments appear to be:

(*a*) The *Staphylococcus albus* is often present as a normal inhabitant of the omentum.

(*b*) The presence of non-bacterial substances injected into the peritoneal cavity appears to increase its activity there in the majority of cases.

One of us has cultivated the same white coccus from the omentum in many cases in which the peritoneum was opened apart from peritonitis. In all these cases the pieces of omentum were dropped into culture-tubes of broth and the growth investigated in the usual way.

### *The finely granular polynuclear cell.*

*The blood.*—One of the most constant phenomena in inflammatory and suppurative lesions both in man and animals is the increase in the number of the finely granular polynuclear cells in the blood.

In our experiments we have found that within a period of fifteen minutes from the time of inoculation the total number per c.mm. of these cells is increased in every instance, while the percentage figure is increased in nine instances out of thirteen. This fact illustrates the rapidity with which these cells accumulate in the blood after an intra-peritoneal injection. In some of the later experiments the increase in the number of these cells has been very striking.

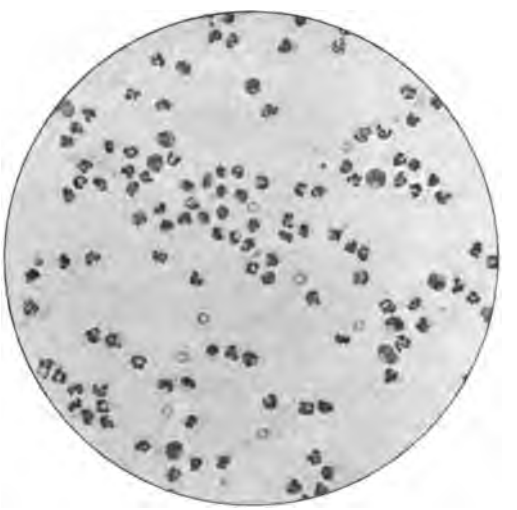
In animals inoculated with the *B. coli* having previously received a subcutaneous injection of opium atypical results were recorded, as was also the case when cultures of the *B. coli* which had previously been killed by heat were injected. For instance, there was a leucopenia both in the percentage and the total number per c.mm. in the two- and four-hours experiments with dead coli, while the absolute number of these cells predominated in the one- and six-hours examples.

In the four-hours coli and opium experiment there was a diminution of these leucocytes both absolute and relative.

*Microxyphilic phagocytosis in the blood.*—We have found this to be a very rare phenomenon. Six hours subsequent to the injection of the *Bacillus pyocyaneus* six finely granular polynuclear cells, out of a total of 500 leucocytes, were seen to contain bacilli. These cells were very much degenerated. In the six hours experiment with the pneumococcus six of these leucocytes out of 500 contained diplococci and were also very much degenerated.

*The phagocytic properties of the finely granular polynuclear cells in the peritoneal exudate.*—It is hardly necessary to point out that these leucocytes, to which Metschnikoff gave the name

FIG. 25.



Peritoneal exudate two hours after the injection of nucleic acid, showing cells of which the large majority are of the finely granular polynuclear kind.

EXPLICATIO FIGURÆ.

Exudatio postquam acidum nucleicum in cavum abdominale injectum erat; ex cellulis polymorphonucleatis minute granulosis, sive neutrophilis, præcipue constat.

"microphages," are of the utmost importance in all inflammatory and suppurative lesions, and are extremely active phagocytes.

We have found that one hour subsequent to an injection of bacteria, toxins, or non-bacterial substances these cells begin to take an important part in peritoneal phagocytosis. Durham has noted that the arrival of these cells in the peritoneal exudate generally marks the termination of the leucopenic

stage in these infections. He has found that it lasts for about five minutes to one hour, but we should be inclined to consider at the end of one hour from the time of inoculation that these leucocytes are generally abundant, as has been stated elsewhere in this communication.

Durham, who has divided up peritoneal infection into various stages, considers that the microxyphile cycle commences at the end of the leucopenic period and terminates in fifteen or sixteen hours after injection, with the arrival of the macrophages of Metschnikoff.

We consider that the microxyphile period in our experiments lasts from about one hour after inoculation up to the death of the animal in the fatal cases of peritonitis, and that the finely granular polynuclear cell is certainly the chief phagocyte within the longest time limit of all our experiments.

The peritoneal fluid in most of our cases, with the exception of two (*B. coli* and *B. pyocyaneus*), diminishes from six hours onwards and was frequently almost absent in the seventeen to twenty-four hours experiments.

In those infections due to the *B. coli* and the *B. pyocyaneus* we noted at the end of twenty-four hours from the time of inoculation that there was marked evidence of peritonitis, and a large quantity of turbid, sticky fluid was found, with abundant deposit of purulent material on the great omentum, under surface of the diaphragm, and upper surface of the liver.

Both finely granular polynuclear cells and bacilli were present in enormous numbers throughout the peritoneal cavity, but especially on the great omentum. We may quote a few examples to illustrate this point, and express our results in a tabulated form.

*Peritoneal exudate* (17—24 *hours after inoculation*).

| Nature of infection. | Time. | Number of finely granular polynuclear cells. | Number of cells found to be phagocytic. |
|---|---|---|---|
| *B. typhosus* . . . . | 17 hours | 489 = 97·8 per cent. | 3 |
| *B. coli* (dead) . . . | 17 „ | 488 = 97·6 „ | 0 |
| *Staphylococcus aureus* . . | 18 „ | 460 = 92 „ | 151 |
| *B. coli* . . . . . | 17 „ | 460 = 92 „ | 459 |
| Nucleic acid . . . | 24 „ | 410 = 82 „ | 0 |
| *Streptococcus pyogenes* . . | 24 „ | 399 = 79·8 „ | 0 |
| Chalk . . . . . | 24 „ | 390 = 75 „ | 55 |

It will thus be seen that although the finely granular polynuclear cells were present in the peritoneal exudate in such large numbers, yet the phagocytic property of this leucocyte was very variable. If, however, the great omentum is examined it is found that the finely granular leucocyte is present in either as large or larger numbers than in the peritoneal exudate, while positive evidence of phagocytosis is very marked, as Durham has also shown to be the case.

*Agglutination of the microphages.*—Durham has alluded to the "balling" of the hyaline cells and the megoxyphils in the preleucopenic period of peritoneal infection, to which we shall refer later.

The agglutination, however, of the finely granular leucocytes into small and large masses was well illustrated in many of our experiments, more especially in the latest periods of the inflammatory processes. Some of the larger "clumps" contained enormous masses of cells easily visible to the naked eye in hanging drop preparations of the peritoneal exudate; perhaps the best instance illustrating this condition occurred in the six-hours guinea-pig which had received an injection of *B. coli* subsequent to opium hypodermically.

*The mononuclear cells in the blood.*—These cells appear to take no part in inflammatory and suppurative infections. In very many instances we have observed in the blood of the guinea-pig that the large mononuclear cells were vacuolated, but we have not classified these cells separately, as in our opinion it is quite unnecessary. If the vacuoles are carefully examined with an oil immersion lens, a central dot will be found in many instances the nature of which we were unable to determine. *Actual ingestion of red blood corpuscles by the large hyaline cells was noted in some cases.* Professor A. E. Wright has drawn attention to a similar phenomenon in two cases of pneumococcic infection in man, and attributes it to the action of the toxin by lowering the vitality of the red blood corpuscles. We, however, have very rarely seen such a condition in the *blood* of man or animals.

*The phagocytic properties of the macrophages.*—Kanthack and Hardy have maintained that actual phagocytosis is effected by the large hyaline cells and that this phenomenon commences at a much earlier period than is usually supposed. It is at its

maximum about twenty-five minutes after the injection of micro-organisms into the peritoneum. We have observed throughout our experiments that the phagocytic properties of the macrophages are constant, but are more especially marked at the earliest and later stages.

Two guinea-pigs inoculated with the *bacillus coli* (after a previous hypodermic injection of opium) were killed respectively fifteen and thirty minutes later. Numerous endothelial cells, which were all phagocytic, were found in the peritoneal exudate in the former instance, while in the latter example they amounted to 86 per cent. out of 500 cells, and no less than 145 of these were phagocytic. In the case of the fifteen-minutes pneumococcus rabbit, the endothelial cells were present in enormous numbers (352, or 70·4 per cent.) but only one cell showed evidence of phagocytosis. The fifteen-minutes streptococcus rabbit was another example; here 91 per cent. of endothelial cells were present in the peritoneal exudate, but none were phagocytic. In the later experiments the macrophages were often found to be numerous, amounting to 20·3 per cent. in the twenty-four-hours experiment with chalk, 15·8 per cent. in the same period after inoculation with the *bacillus pyocyaneus* and several other instances referred to in the tables.

It is necessary, however, to be certain that the endothelial cells are really present in the peritoneal exudate, and not simply rubbed off the surface of the peritoneum during the operative procedures. This unfortunate accident is only likely to happen in those instances in which fluid is very scanty.

Metschnikoff has demonstrated that one of the main functions of the macrophages is their power of devouring the microphages, micro-organisms, and various other substances. We have occasionally observed in the latest experiments two or three microphages (containing micro-organisms) ingested within the macrophages, but within the period of twenty-four hours, which was not exceeded in our experiments; this phenomenon of ingestion of the micro- by the macrophages was not by any means as common as many observers have maintained.

*Agglutination of the mononuclear cells in the peritoneal exudate.*—We are in accordance with the observation made by Durham that agglutination of the large mononuclear cells is of constant occurrence in the peritoneal fluid in the earliest period of

peritoneal infection, but the small lymphoid cell is exempt. In some instances large clumps of the large mononuclear cells were formed.

*The nature and the origin of the coarsely granular eosinophiles.*—It is necessary to say a few words on these leucocytes, which are found in almost every tissue of the body in man and animals, which collect in the tissues in large numbers in most cases of helminthiasis and certain other conditions, and which we have shown to be present in very large numbers in the peritoneal exudate in the very early stages of infection.

It is also recognised that they accumulate in large numbers in certain new formations, to which the term "eosinophilic granulomata" has been applied, while they are by no means rarely seen in great numbers in malignant tumours of the lip and in certain other situations.

Ehrlich considered that the seat of origin of these cells was the bone-marrow, but other observers have drawn attention to their presence in large numbers in other tissues and have suggested that the seat of origin may be found outside the marrow. Siawcillo has found them to be numerous in the villi of the intestine and in the conjunctival mucosa. Dudgeon has found every variety of eosinophile in large numbers in the thymus glands of children; others have found them to be numerous in the spleen, hæmolymph glands, and in the lymphatic glands. It has been stated that the coarsely granular cell under certain conditions is derived from the finely granular cell, and that we may meet with transitional forms containing both types of granules, but reliable observations on this point are lacking.

Siawcillo considers Ehrlich's view, that the coarsely granular eosinophile cell is derived from the bone-marrow, is too general a statement to be universally accepted. He has found that there are large numbers of these leucocytes in the skate, but there is an absence of bone-marrow.

*The nature of the granules.*—Siawcillo has stated that these granules are readily investigated by micro-chemical tests, and that they are formed of albuminous substances. Ehrlich, as is well known, regards the megoxyphile as a gland containing secretory granules.

*The coarsely granular eosinophile cells in the blood.*—We are in entire accordance with Dr. Opie's view, that "the percentage

of eosinophilic leucocytes in the blood of apparently healthy guinea-pigs is subject to great variation, the percentage count ranging from less than one to more than fifty.

We, however, as already stated, have always examined the blood both before and after each experiment, and have, therefore, avoided conclusions drawn from pathological phenomena alone. It is now a well-established fact that the coarsely granular eosinophile cell rapidly diminishes in number, and frequently disappears from the blood during the course of acute inflammatory and suppurative lesions in man and in animals. But some observers have shown that this variety of leucocyte may reappear in the blood, and even be fairly numerous, during the period of convalescence.

In most instances we have found that these cells are both relatively and absolutely diminished from four hours onwards. There are, however, exceptions to this statement. In the experiments with the pneumococcus there was an absolute and relative increase in the numbers of the coarsely granular eosinophiles, except in the example of the forty-hours rabbit, in which they were absent from the pathological blood. Again, in the case of the guinea-pigs inoculated with the *B. coli* these cells were both absolutely and relatively increased in every experiment.

It is of interest to note that there was both a relative and absolute increase in some examples within the first 120 minutes from the time of inoculation.

*The phagocytic properties of the coarsely granular eosinophile cells.*—The main question that we have to ask regarding the coarsely granular eosinophile cell is whether this leucocyte plays any part in actual phagocytosis. The answer which most observers have given has been in the negative, while a few have brought forward just sufficient evidence to prove that they possess this property, but only in the very slightest degree.

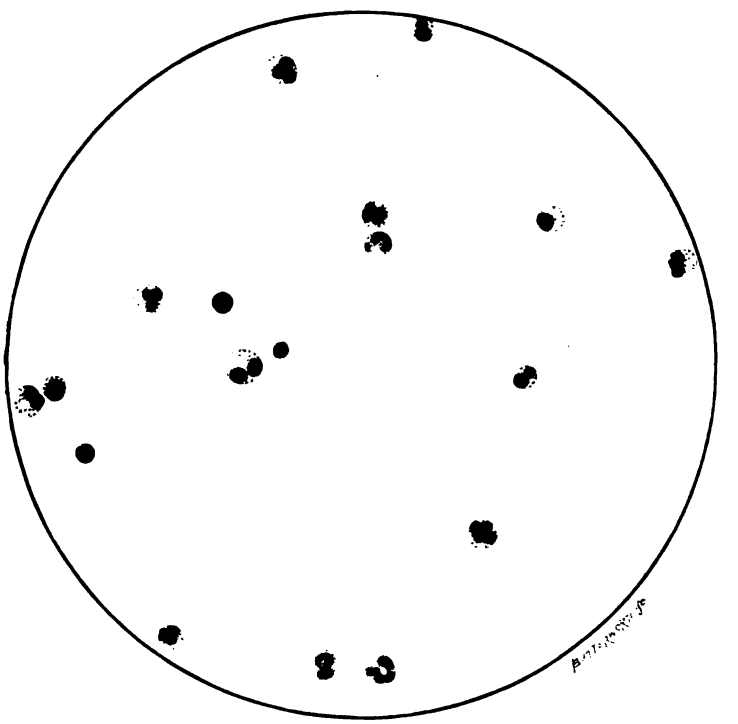
Mesnil considers that, although this leucocyte is already filled with nutritive material, it does in some cases actually ingest micro-organisms. "I have several times seen it in the exudate of the lymphatic dorsal sac of the frog after the injection of micro-organisms."

He has described a case of a frog inoculated by the intra-vascular route where this phenomenon was frequently present in

the liver, but especially in the kidney; and he states that he has seen micro-organisms absorbed by the coarsely granular cell and to show an affinity for eosin.

Durham has failed to observe any true or apparent loss of

FIG. 26.



Peritoneal exudate, fifteen minutes after the intra-peritoneal injection of nucleic acid. It contains a large percentage (41·6) of coarsely granular eosinophile cells.

EXPLICATIO FIGURÆ.

Exudatio post partem horæ quartam indagata postquam liquor acidi nucleici in cavum abdominali injecta erat. Monstrantur plurimi leucocyti eosinophili (41·6 per centum).

granulation in these cells as a result of contact with bacteria; but on one occasion he observed a megoxyphile cell with an ingested bacillus contained within a vacuole. "The size of the microbe and the distinctness of its inclusion allowed no possibility of doubt that this form of leucocyte can be phagocytic."

Opie in a recent paper on this subject stated that "the

eosinophile leucocytes, like the finely granular polynuclear leucocytes, accumulate in the neighbourhood of bacteria injected into the body, and though they rarely act as phagocytes, play a part in the series of changes which follow bacterial invasion."

Hektoen states that the coarsely granular eosinophile cells never act as phagocytes, yet they are present in relatively large numbers in inflammatory exudates. Hankin, who maintained that the coarsely granular eosinophile was phagocytic in the rabbit, was shown by Metschnikoff to have mistaken this cell for the finely granular polymorphonuclear leucocyte.

Kanthack and Hardy have claimed that the first cell attracted by micro-organisms and irritants injected into the peritoneal cavity is the coarsely granular eosinophile. Subsequent to the injection of the *B. anthracis* and of the *cholera spirillum* into the peritoneum no cells other than coarsely granular eosinophiles were seen for seven hours—a statement which will not bear investigation.

We have failed to observe the preliminary discharge of granules on the part of the coarsely granular eosinophiles during peritoneal infection, but we have noted that some of these cells, which were phagocytic, contained fewer granules than those in the normal condition.

We have observed that the coarsely granular eosinophile cell is extremely numerous within the first two hours of peritoneal infections, amounting in one instance, as recorded in the above table, to no less than 82 per cent. of the cells. In hanging drop preparations of the peritoneal exudate we noted this phagocytic action, while in film preparations from the fluid micro-organisms were seen to have been ingested.

It has been stated by some authorities that micro-organisms, although attacked by the coarsely granular eosinophiles, are not really taken into their interior. In those instances in which bacteria appear to be within the cell they are really on its surface; the true evidence of phagocytosis, according to Durham, viz. a vacuole around the ingested organism, being wanting. Still further, some observers would have us believe that the nature of the eosinophile cell is not that of a phagocyte, but mainly to discharge its granules into the serum in the early stages of inflammatory infections. We have seen that the megoxyphils in the peritoneal exudate are by no means rarely vacuolated and

*List of experiments in which the coarsely granular eosinophile cells amounted to over 15 per cent. of the cells present in the peritoneal exudate.*

| Nature of inoculation. | Hours. | Total number of cells counted. | Percentage of eosins. | Coarsely granular eosinophile cells with micro-organisms or non-bacterial substances contained within them. |
|---|---|---|---|---|
| Chalk | 15 minutes | 400 | 37·25 | 83 |
| *Bacillus coli* (dead) | 2 hours | 400 | 62·0 | 93 |
| *Bacillus pyocyaneus* | 1 hour | 500 | 37·4 | 148 |
| „ „ | 2 hours | 500 | 41·2 | 199 |
| Nucleic acid | 15 minutes | 500 | 41·6 | — |
| „ „ | 2 hours | 500 | 49·2 | — |
| Normal saline solution | 1 hour | 400 | 76·5 | — |
| „ „ „ | 2 hours | 500 | 31·4 | — |
| Toxins of *B. pyocyaneus* | 1 hour | 500 | 15·4 | — |
| *Bacillus coli* | 15 minutes | 500 | 75·8 | 16 |
| „ „ | 2 hours | 500 | 82·2 | 208 |
| „ „ | 4 hours | 500 | 71·0 | 246 |
| *Staphylococcus albus* | 15 minutes | 400 | 54·0 | 131 |
| „ „ | 2 hours | 500 | 15·6 | 44 |
| *Bacillus coli* + opium | 15 minutes | 400 | 72·5 | 155 |
| „ „ „ | 1 hour | 400 | 27·25 | 80 |
| „ „ „ | 2 hours | 500 | 39·8 | 176 |
| „ „ „ | 4 hours | 500 | 21·4 | 77 |
| „ „ „ | 6 hours | 400 | 40·5 | 162 |
| Pneumococcus | 1 hour | 500 | 15·6 | — |

that vacuoles have been seen in some instances surrounding the ingested micro-organisms. We have constantly observed that ingested bacteria showed very marked structural changes and alterations in their staining reactions.

Included bacilli were beaded, considerably swollen, and had an irregular outline in comparison with the micro-organisms in the surrounding exudate. We see no reason to believe that these leucocytes possess no phagocytic properties and that the micro-organisms and other substances are merely lying on the surface of the cells.

Our observations, however, on this point have been especially framed with the view of endeavouring to settle this important question. If we are to allow that all bacteria which appear to be ingested are merely on the surface of the cell, we are presented with a very difficult problem. We have no hesitation in estimating the amount of phagocytosis in every other variety of leucocyte, and it is seldom questioned that the bacteria which *appear*

## DESCRIPTION OF PLATE II,

### Illustrating the communication on "Phagocytosis" by Mr. L. S. Dudgeon and Dr. Athole Ross. (P. 155.)

FIG. 1.—Film preparations of peritoneal exudate stained by Leishman's method. In the left half of the figure there are shown four coarsely granular, eosinophile leucocytes with ingested micrococci. The cells were found present in the exudate fifteen minutes after the intra-peritoneal injection of the *Staphylococcus pyogenes albus*. In the right half of the figure is shown a similar film in which the *Bacillus coli* has been taken up by similar cells two hours after the injection. The differences in size of the intra- and extra-cellular micro-organisms and in their mode of staining are noteworthy. ($\frac{1}{12}$ + Oc. B.)

FIG. 2.—A streak-film preparation of marrow (femur) stained by Leishman's method. The preparation was made two hours after the injection of the pneumococcus into the peritoneal cavity of a rabbit. The nucleated red cells are in conspicuous numbers; the predominance of the non-granular lymphoid type of cell is also shown.

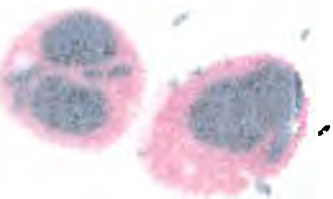
## TABULA II,

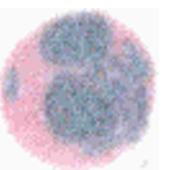
### ad dissertationem de "Phagocytose" illustrandam.

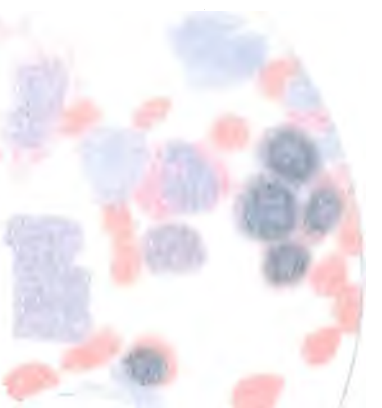
### L. S. Dudgeon; A. Ross. (P. 155.)

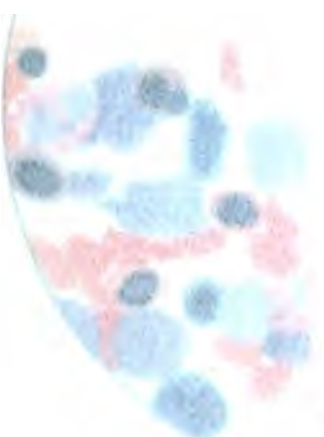
FIGURA 1.—In parte sinistrâ monstrantur in exudatione intraperitoneali cuniculi quattuor leucocyti eosinophili cum granulis crassis, in quibus micrococci clausi sunt postquam cultura *Streptococci pyogenis albi* in cavum abdominale injecta erat. Examinata est exudatio post horæ partem quartam. In parte dextrâ monstrantur quattuor leucocyti eosinophili cum granulis crassis, in quibus *Bacilli coli* clausi sunt. Examinata est exudatio post horas duas. Bacilli in cellulis clausi insigniter tumuerunt.

FIGURA 2.—Ossium medulla (cuniculi femoris). Examinata est medulla horâ secundâ postquam cultura pneumococci in cavum abdominale injecta erat. Erythrocyti nucleati atque cellulæ generis lymphoidis plurimi adsunt.









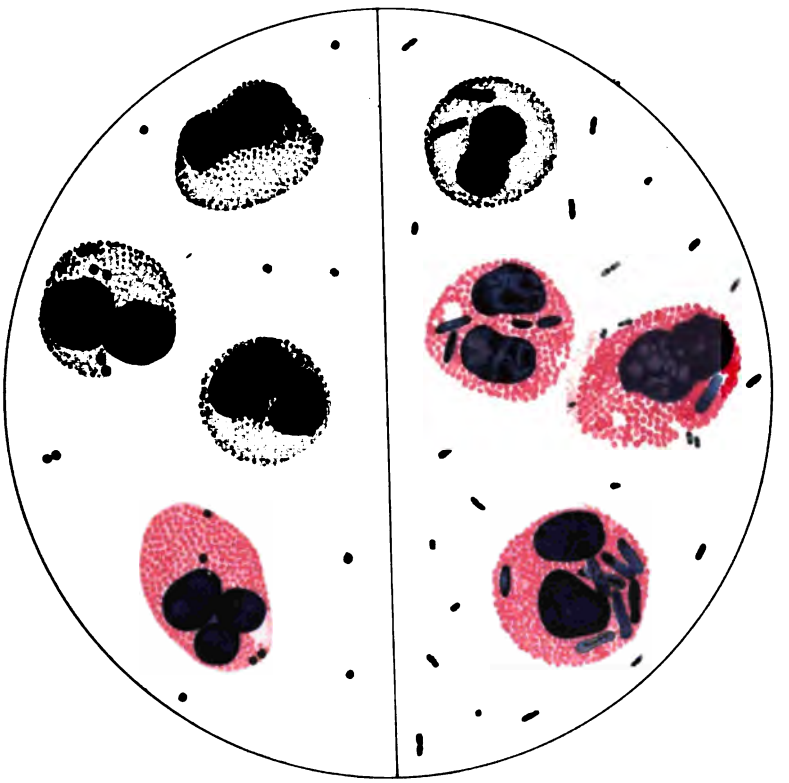


Fig. 1.

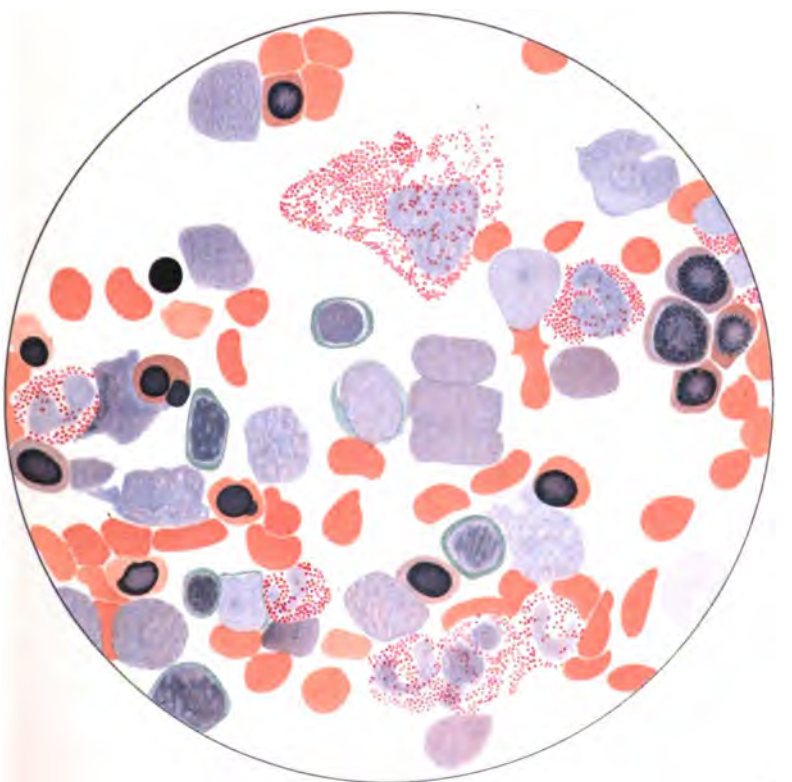


Fig 2.

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to be within the cells, whether surrounded by a vacuole or not, are really so.

In conclusion, how would it be possible to estimate the phagocytic property of the blood by the most recent methods if we are to take the presence of a vacuole surrounding the organism as the only true evidence of phagocytosis? We have, however, referred to this point at the commencement of this communication.

### *The bone-marrow.*

*The normal marrow.*—Prof. Muir gives the following account of the white cells in the normal bone-marrow:

(1) The majority of the cellular elements are of the finely granular type (neutrophilic in man and amphophilic in the rabbit).

(2) A smaller group of cells with coarsely staining eosinophile granules are found.

(3) Hyaline or non-granular cells and giant cells are also present.

He has stated that the finely granular cells multiply the most actively and show a maximum of mitotic figures, while this feature is less evident in the coarsely granular eosinophile leucocytes. Muir very rightly insisted that the term "myelocyte" should be understood to mean a *granular cell or cell in which the presence of distinct granules may be regarded as histologically proved.* A perusal of the literature will bring to light many instances in which too loose an interpretation has been given to this term.

In Dr. C. Price-Jones's paper dealing with the influence of certain micro-organisms on the cellular constitutents of the bone-marrow the following percentages are given for the various cells present in the normal marrow of man, the rabbit, and the guinea-pig.

| | Man. | Rabbit. | Guinea-pig. |
|---|---|---|---|
| Lymphoid cells . . . . . | 50·4 | 51·3 | 43·3 |
| Granular cells . . . . . | 49·5 | 48·4 | 56·2 |
| Nucleated red cells . . . . | 8·2 | 11·7 | 8·04 |

By the term "granular cell" Dr. Jones refers to the "myelocyte" and cells intermediate between the myelocyte and the polynuclear cells. We have recognised many varieties of granular cells, viz. neutrophilic, eosinophilic, basophilic, and amphophilic myelocytes, polynuclear cells and cells intermediate between these and the myelocytes. It is rather unfortunate that we have only examined pathological bone-marrows, but from what we have found in our normal saline series of guinea-pigs we are in agreement with the observations of Prof. Muir and Dr. Price-Jones on physiological bone-marrow. In the above-mentioned examples we noticed that the non-granular type of cell was not so numerous in the marrow as was the case in most of the other series. We may, therefore, conclude that "myelocytes" are fairly numerous in healthy marrow, especially if we allow for the fact that the injection of normal saline solution produced an increase of the polymorphonuclear elements in the blood, which would, according to Muir, involve a corresponding drain on the mother cells in the bone-marrow. It may thus be legitimately urged that the constant increase of non-granular cells which we have found in the very early stages of acute infective conditions is a strictly pathological phenomenon. Moreover, in several of our fifteen-minutes experiments before sufficient time had elapsed for pathological changes to become evident we have found the myelocytic type of marrow.

*On the cytology of the bone-marrow in acute infections.*—In his researches on the bone-marrow in certain acute infective diseases Muir came to the following conclusions:

(1) There is an important increase in the numbers and activity of the neutrophilic myelocytes which he called the "neutrophile reaction."

(2) In severe affections a leucopenia occurs, and there is a depletion of the marrow, with an appearance of its elements in the blood-stream.

(3) The formative function of the marrow is greatly increased in infections, but there is little phagocytosis on the part of its cells.

(4) Mitosis frequently occurs.

We have always carefully looked for evidence of phagocytosis in our marrow films, but we have never seen it. There can be little doubt that the bone-marrow takes an unimportant share in actual phagocytosis.

Prof. Muir has examined the marrow in seventy cases, including empyema, acute pneumonia, and smallpox. We cannot too strongly insist that this author's conclusions are not in any way comparable to ours, because in his cases the acute infective process had continued for many days, instead of only a few hours as in our own experiments.

In our research the shortest interval was fifteen minutes and the longest but little more than twenty-four hours; moreover as far as we know no previous observer, with the exception of Dr. Price-Jones, has investigated this subject at so early a stage. It is, therefore, not surprising that our results should differ from those of other workers. In spite of this fact the results of Prof. Muir's observations on the bone-marrow in his *rapidly fatal* cases of hæmorrhagic smallpox agree somewhat closely with our own. In these instances he has found that although a certain amount of neutrophile reaction may be present, it is usually absent or diminished, and the number of neutrophilic myelocytes is considerably reduced, while few mitotic figures are to be seen.

In other words, the non-granular cell is the important element in the bone-marrow during the *very early stages* of acute infective conditions. This is what we have found to be nearly always the case throughout our researches. The exceptions were the six- and twenty-four-hours examples of the *staphylococcus aureus,* where the marrow was of the myelocyte type. There appears to be no material difference between the findings in the marrow of a person dead from a *rapidly fatal* disease, such as hæmorrhagic smallpox, and what can be demonstrated in the marrow of rabbits and guinea-pigs in the *early stages* of acute infective conditions. Prof. Muir found that the most marked neutrophile reaction occurred in rabbits inoculated with the pneumococcus subcutaneously and killed in four weeks.

Dr. Jones, experimenting on rabbits with the pneumococcus, shows very clearly how great an influence the duration of the experiment has on the type of marrow produced. In one series of rabbits inoculated intra-peritoneally with the pneumococcus the animals were *nearly all dead within twenty-four hours,* and it was found that the marrow was "lymphoblastic" or that the non-granular cell predominated. In a second series the inoculation was subcutaneous; here the animals survived *for about five days* and a leucoblastic type of marrow was obtained. In other

words, he found the "non-granular" cells to be the most important variety in the early stages of infection and the "granular cells" in the later stages.

We venture to think that we could hardly want stronger evidence of the great importance of the non-granular mononuclear cell in the early stages of pneumococcic infection. In our experiments we found a lymphoid type of marrow after intra-peritoneal inoculation with the pneumococcus from one hour up to and including six hours. We have never, however, seen a mitotic figure in any single instance, while Prof. Muir has frequently observed them. In our cases the probability is that there has not been sufficient time for the giant cells to exhibit those degenerative changes so often observed by Muir.

As regards the coarsely granular eosinophilic varieties of myelocytes, we are quite of Prof. Muir's opinion, that they form a less important group in the cytology of the bone-marrow in nearly all cases. We must, however, draw attention to the fact that the bone-marrow of the guinea-pig which died twenty-four hours after an intra-peritoneal injection of the *bacillus aerogenes capsulatus* showed 34·6 per cent. of the coarsely granular eosinophilic class of leucocyte, but the blood in this instance showed a distinct megoxyphilia.

*The finely granular polynuclear cells.*—In the large majority of cases these cells appear to form only a very small proportion of the cellular constituents of the bone-marrow in our experiments. In only sixteen instances out of the grand total did they amount to five per cent. or more of all the cells present, while in the majority of instances they occurred in infinitesimally small numbers. In a few examples, however, they were present in a very large proportion. We may best illustrate this fact by expressing it in tabular form:

| Nature of infection. | Time of experiment. | Percentage. | Total number of cells counted. |
|---|---|---|---|
| Dead coli | 1 hour | 28·6 | 1000 |
| „ „ | 24 hours | 13·3 | 1000 |
| *Staphylococcus aureus* | 18 hours | 12·4 | 500 |
| *Bacillus coli* | 1 hour | 12·7 | 1000 |
| „ *typhosus* | 4 hours | 16·2 | 1000 |
| „ *aerogenes capsulatus* | 1 hour | 23·0 | 1000 |
| „ „ „ | 24 hours | 24·3 | 300 |
| Pneumococcus | 1 hour | 11·0 | 1000 |
| *Bacillus coli* + opium | 30 minutes | 15·1 | 1000 |

These observations fully coincide with the results obtained by Dr. Price-Jones, who has remarked on the scarcity of these cells in the bone-marrow of acute infective processes. The paucity of the finely granular polynuclear cell in the bone-marrow under these conditions is of very great interest, when we consider that it is the important phagocyte in the tissues, blood, and other body fluids in every inflammatory process invoked by pathogenic organisms.

*On erythroblastic marrow.*—There is little doubt that a megaloblastic type of marrow can be produced in man by various toxic agencies, and especially by the disease known as progressive pernicious anæmia. These facts, however, do not concern us in the present research.

We have found that large numbers of nucleated red cells are present in the marrow of rabbits and guinea-pigs consequent upon the injection of pathogenic organisms and certain non-bacterial substances. In some instances as large a number of nucleated red cells are found in the bone-marrow of animals as are seen in man, even in pernicious anæmia. It appears that the injection of the pneumococcus or the *streptococcus pyogenes* into rabbits is especially prone to produce this effect. One hour subsequent to the intra-peritoneal injection of the *streptococcus pyogenes* into a rabbit, no less than 160 normoblasts, 118 megaloblasts, and 59 gigantoblasts were seen while counting 1,000 leucocytes, which is equivalent to slightly more than 33 per cent. of the total number of cells.

In the four-hours experiment 174 normoblasts, 55 megaloblasts, and 7 gigantoblasts were recorded while enumerating 1,000 white cells, which is equivalent to 23 per cent. of the entire number of cells. Two hours after the injection of the pneumococcus 118 normoblasts and 63 megaloblasts were noted during a count of 1,000 leucocytes, which is equivalent to 23 per cent. It is unnecessary to dwell further on facts which are so obvious and which have been fully described elsewhere in this communication. In many of these experiments large numbers of nucleated red cells were counted in the bone-marrow, but the three examples to which we have just referred are the best marked instances of erythroblastic marrow. Of course we have to allow for many nucleated red cells being present in so-called normal bone-marrow. We have found that this phenomenon is constantly associated with a lymphoblastic type of marrow.

Dr. Price-Jones, from a record of intra-peritoneal inoculations with the pneumococcus into rabbits, death supervening within twenty-four hours, found, from an average of thirteen experiments, that the lymphocytes averaged 61 per cent., granular cells 38 per cent., and nucleated red cells 35 per cent. This variety of bone-marrow he describes as the lympho-erythroblastic type.

Although the bone-marrow in these experiments to which we have just referred was of the erythroblastic type, yet nucleated red cells in the blood were seldom seen.

Dudgeon and Turney have also recorded an instance of a lympho-erythroblastic marrow in a case of lipæmia which terminated from acute pneumonia within four days.

**Summary of experiments with normal saline solution.**

*The blood. The number of leucocytes per c.mm.*—In every instance a leucocytosis occurred; in most instances it was only slight, but in one example, the two-hours experiment, a pathological leucocytosis occurred which amounted to 4,200 per c.mm. more than in the physiological blood.

*Differential leucocyte count.*

*The finely granular polynuclear cells* were absolutely increased in every instance, especially in the case in which the animal was killed one hour after the injection of the normal saline. Here these cells totalled 72 per cent. and 3,456 per c.mm. as against 31·2 per cent. and 961 per c.mm. in the physiological blood. In the twenty-four-hours experiment the finely granular polynuclear cells were diminished relatively but increased absolutely.

*The coarsely granular eosinophiles* were increased both relatively and absolutely in the three earliest experiments, whilst they were diminished both absolutely and relatively in the last three experiments. In one instance large numbers of these cells were found, 11 per cent., or 814 per c.mm., as against 2·5 per cent., or 80 per c.mm., in the physiological blood.

*The mononuclear cells.*—No constant changes were found in any of these cases.

*The peritoneal exudate.*—In the quarter-hour and in the

one-hour experiment the exudate was present in large amount, but after that period only a small quantity was found.

*The cells.—The coarsely granular eosinophile* was found to be the most common type of cell in the peritoneal exudate in the one-hour case, amounting to no less than 76·5 per cent. out of a total of 400 cells. In the two-hours example they were still numerous, but very much less so; here they came to 31·4 per cent., but in the later experiments they were only present in very small numbers.

*The mononuclear cells.*—In the quarter-hour case the mononuclears came to 95·6 per cent. of the cells, in the one-hour 22·50 per cent, in the two-hours 37·4 per cent., and afterwards they gradually diminished.

*The finely granular polynuclear cells* from the two-hour experiment onwards was the most important peritoneal phagocyte. In the last three cases they amounted to over 80 per cent.

*The bone-marrow.*—No nucleated red cells, or only one or two, were seen in the various specimens of marrow, except in the two-hours case, in which four normoblasts and two megaloblasts were seen while counting 500 white cells. The non-granular mononuclear cells were very scanty in this instance.

No constant changes were observed in the white cells of the bone-marrow as a result of the injection of normal saline.

*Summary of experiments with the toxins of the B. pyocyaneus.*

*The blood. Total number of leucocytes per c.mm.*—A pathological leucocytosis occurred in every case in these experiments. The leucocytosis was only slight, however, the greatest excess amounting to 2,200 per c.mm. in the blood of the four-hours guinea-pig.

*Differential leucocyte count.—The finely granular polynuclear cells* were increased absolutely in every instance and relatively in all but the quarter-hour case. The greatest excess was found in the four-hours experiment—a relative excess of 47·4 per cent. and an absolute gain of 3,530 per c.mm.

*The coarsely granular eosinophiles* did not show any noteworthy changes. In one animal, the four-hours guinea-pig, however, the blood was of interest. We found 920 of these cells per c.mm., or 23·4 per cent., in the physiological blood, while in

the pathological blood, as one would expect, a considerable reduction had taken place—434 per c.mm., or 7·4 per cent.

*The mononuclear cells* did not show any constant changes.

*The erythrocytes.*—In the pathological blood of the two-hours guinea-pig one normoblast was seen, and in the pathological blood of the twenty-four-hours animal one megaloblast and three normoblasts were found.

Polychromatophilia was well shown in the blood of the latter animal. *In a few instances some of the large mononuclear cells appeared to contain red blood corpuscles.*

*The peritoneal exudate.*—In the first three animals used in these experiments the peritoneal fluid was found to be clear and in large amount. In the fourth case it was abundant but turbid, in the fifth it was very scarce, and in the last instance none was seen.

Slight cell agglutination was observed in three instances, while in the four-hours experiment the clumps were large.

*The cells.—The coarsely granular eosinophiles* were present in large numbers in one of the cases—the one-hour experiment. In the exudate obtained from this animal 15·4 per cent. of the phagocytes belonged to this class.

*The small mononuclear cells* were the most numerous phagocytes in the peritoneal exudate of the quarter-hour and six-hours animals. In the former instance they amounted to 97·4 per cent. out of a total of 195 and in the latter example they totalled 78·8 per cent. out of 500. In the one-hour experiment the small mononuclear cells were also present in large numbers, 54·2 per cent. out of a total of 500.

*The finely granular polynuclear cells* were the most important phagocytes in the peritoneal exudate, except in the cases in which the small mononuclear cells predominated, viz. the quarter-hour and the six-hours animals. In the two-hours experiment they formed no less than 94·8 per cent. out of a total of 500 cells counted.

We are unable to explain, however, why in the instance of the six-hours guinea-pig the small mononuclear cells should amount to 78·8 per cent. of the cells and the finely granular polynuclear cells only 5·2 per cent., while they should total 88·2 per cent. and 88 per cent. in the experiment preceding and following this one.

*The bone-marrow.*—The small and large non-granular mononuclear cells were markedly increased in the twenty-four hours experiment as compared to the quarter of an hour. In the former instance they amounted to 73·2 per cent. of all the white cells in the bone-marrow, while in the latter example they only amounted to 56·6 per cent., an increase of 16·6 per cent. In the six-hours case they amounted to 68 per cent. We must remember, however, that 64·6 per cent. of the cells in the bone-marrow in the two-hours experiment were of this class, while in the four-hours case only 52·2 per cent. were mononuclears. The neutrophilic myelocytes diminished from over 20 per cent. in the earlier cases to 1·7 per cent. in the twenty-four-hours guinea-pig. Large numbers of nucleated red cells were seen in the bone-marrow in the three latest experiments, while none were seen in the earliest. Thirteen normoblasts and one megaloblast were counted in the marrow of the four-hours guinea-pig, fifteen normoblasts and one megaloblast in the six-hours case, and three megaloblasts and one normoblast in the twenty-four-hours animal.

*Summary of experiments with nucleic acid.*

*The blood. Total number of leucocytes per c.mm.*—There was a pathological leucocytosis in every case, without exception. The greatest leucocytosis amounted to 4,000 per c.mm.

*Differential leucocyte count.*—There was an increase, both absolute and relative, of *the finely granular polynuclear cells* in the pathological blood in every instance. The greatest excess occurred in the six-hours example; here they amounted to 75·6 per cent. and 6,688 per c.mm. as against 10·6 per cent. and 528 per c.mm. in the physiological blood.

*The coarsely granular eosinophiles* varied to such an extent as to show that the number of these cells bore no relation to the nature of the experiment.

*The mononuclear cells* gave no constant changes.

*The erythrocytes.*—Well-marked alterations in the red cells occurred in both the physiological and pathological blood of the six-hours case. Three normoblasts were seen while counting 500 leucocytes in the physiological blood and two normoblasts and one megaloblast in the pathological blood. In each instance severe poikilocytosis and polychromatophilia were present.

*The peritoneal exudate.*—This was present in large quantities in the first four experiments, but only in slight amount in the remaining two. The appearances of the peritoneum were normal. Large numbers of phagocytes were found in the exudate in the last four experiments.

*The cells.—The coarsely granular eosinophiles* were numerous in the first three experiments—41·6 per cent. in the quarter-hour case, 12·2 per cent. in the one-hour, while in the two-hours case they totalled 49·2 per cent.

*The small mononuclear cells* were most abundant in the first two experiments—39·6 per cent. and 34·6 per cent. respectively; whilst in the last four cases they were found in much smaller numbers, but yet distinctly numerous—9 per cent., 4·8 per cent., 15 per cent., and 17·4 per cent., arranged in regular sequence.

The large mononuclear cells were only numerous in the first experiment (65), in which they totalled 12·8 per cent. out of 500 cells counted.

*The finely granular polynuclear cells* from the one-hour experiment onwards were the most important phagocytes in the peritoneal exudate. In one instance, the four-hours case, they amounted to 94 per cent., or 470 out of the 500 cells counted.

In many instances cell-agglutination was well shown.

*The bone-marrow.*—The small mononuclear cells were much more abundant in the last five experiments than in the first, while in the sixth instance these cells totalled no less than 79·8 per cent. as against 50·2 per cent. in the first case. No other constant changes were found in the white cells in the bone-marrow. Large numbers of nucleated red cells were present in the bone-marrow in every instance, especially so in the six-hours experiment, when three gigantoblasts, six megaloblasts, and thirty-five normoblasts were seen while counting 1,000 cells.

### *Summary of experiments with chalk.*

*The blood. Total number of leucocytes per c.mm.*—In every experiment there was an absolute increase in the number of leucocytes in the blood after an intra-peritoneal injection of a sterile suspension of chalk in normal saline. The greatest leucocytosis, however, was not excessive, only amounting to an increase of 3,300 per c.mm. of blood, in the six-hours experiment.

*Differential leucocyte count.*—There was a relative and absolute increase of the *finely granular polynuclear cells* in every instance in the pathological blood except in the last case, in which there was both a relative and absolute diminution. The greatest increase occurred two hours after injection; here the polynuclear cells amounted to 83·6 per cent. and 5,964 per c.mm. as compared to 48·4 per cent. and 2,496 per c.mm. in the physiological blood.

*The coarsely granular eosinophiles* were both absolutely and relatively diminished in all the experiments, except the first (77), in which they were found to be both absolutely and relatively increased.

*The mononuclear cells* did not show any constant changes.

*The erythrocytes.*—Nothing abnormal was noted.

*The peritoneal exudate.*—The exudate was only once found to be present in large quantity, and that was six hours after inoculation, the same experiment in which there was the most marked leucocytosis and increase of the polynuclear cells.

*The cells.—The coarsely granular eosinophiles* were found to be the most important phagocytes in the first experiment (77)—*i. e.* a quarter of an hour after the injection of chalk. They were present in large numbers—37·25 per cent.—and 83 of the 149 cells which were counted were proved to be phagocytic. In no other experiment was the phagocytic property of the coarsely granular eosinophile cell found to be of any importance.

*The small mononuclear cells* were present in enormous numbers in the two earliest experiments—60·5 per cent.—of which 4 were phagocytic in the first instance (77) fifteen minutes after inoculation, and 93·8 per cent., of which 15 were phagocytic in the second experiment (78) one hour after inoculation, also in the last case (82) in which 20·6 per cent. of these cells were present.

*The finely granular polynuclear cells* were first shown to be important phagocytes in the third experiment (79) and remained so till the last. Two hours after inoculation they amounted to 84·6 per cent. of the cells, and no less than 198 were phagocytic out of a total of 423. These cells were not as numerous, however, in the last instance as in this.

*The great omentum.*—The chalk was seen in abundance entangled in the meshes of the great omentum within one hour

after inoculation and remained so up to and including the last experiment.

*The bone-marrow.*—No constant abnormal changes were noted in the histology of the bone-marrow throughout these experiments with chalk. In one instance (80) nine normoblasts were seen while counting 1,000 leucocytes.

*Summary of experiments with the bacillus coli.*

*The blood. Total number of leucocytes per c.mm.*—The number of the leucocytes per c.mm. showed an increase in the pathological blood of all the experiments after inoculation with the *B. coli* except in experiment 22 (eight hours); here the number of leucocytes in the physiological blood amounted to 5,400 per c.mm. against the pathological blood 2,000 per c.mm. The feature of this leucocytosis was that in every instance it was only moderate. The highest count was in experiment 20 (two hours)—physiological blood 3,000 and pathological blood 4,800 per c.mm. In experiment 21 A (four hours) the moderate leucocytosis was well shown—physiological blood 3,600 and pathological blood 3,800 per cmm.

*The differential leucocyte count.—The finely granular polynuclear cells* in the first six experiments showed an absolute increase in every case (18 to 21 A) and a relative increase also except in experiment 18 (fifteen minutes), in which they were 41 per cent. in the physiological blood as against 34 per cent. in the pathological blood. In experiment 20 A (two hours) and 21 A (four hours) this absolute and relative increase was enormous, for in experiment 20 A the finely granular polynuclear cells were 6 per cent. and 222 per c.mm. in the physiological blood as against 54 per cent. and 2,214 per c.mm. in the pathological blood. A very similar condition was present in experiment 21 A.

In the pathological blood of experiment 22 (eight hours) the finely granular polynuclear cells were relatively and absolutely diminished (37 per cent. and 1,998 per c.mm. in the physiological blood against 26 per cent. and 520 per c.mm. in the pathological blood). The cells were too degenerated to count in the pathological blood of experiment 23 (seventeen hours).

*The coarsely granular polynuclear cells* in six of the experi-

ments were both relatively and absolutely increased in the pathological blood. In most cases the absolute increase was about double the number per c.mm. found in the physiological blood. In experiment 20 (two hours) the relative and absolute increase of these cells was very marked (physiological blood 0·6 per cent. and 18 per c.mm. as against 4 per cent. and 192 per c.mm. in the pathological blood). In experiment 21 (four hours) there was a large relative and absolute decrease in the coarsely granular polynuclear cells of the pathological blood (physiological blood 8 per cent. and 472 per c.mm. as against pathological blood 1 per cent. and 60 per c.mm.).

*The mononuclear cells* of the pathological blood in five experiments showed an absolute decrease quite proportional to the increase of the finely granular polynuclear cells. In experiment 20 (two hours) they were stationary and in experiment 19 (one hour) there was a slight absolute increase in the pathological blood.

Regarding the other cells there was nothing of importance to note. A point of interest is the variability in the mast-cells, which in experiment 21 (four hours) were 3 per cent. and 177 per c.mm. in the physiological blood and were absent from the pathological blood.

*The red cells.*—Usually no change was seen, but in experiment 20 (two hours) polychromatophilic degeneration was noted in the pathological blood.

*The peritoneal exudate.*—As a rule the peritoneal fluid was abundant. The hanging drop preparations usually showed large numbers of bacilli, either motile or non-motile, and the cells were numerous. Degenerative changes in the bacilli were noted in experiment 21 A (four hours) and experiment 23 (seventeen hours). Agglutination of cells (polymorphonuclears) was very marked after four hours (experiment 21) and after one hour, but was only slight after two hours. Clumping of bacilli was noted after one hour. Eight hours and more after inoculation with the *B. coli the finely granular polynuclear cell* seems to be the important phagocyte. In experiment 22 (eight hours) these cells were 58 per cent. and 194 were proved to be phagocytic, and in experiment 23 (seventeen hours) they were 92 per cent. and 459 were phagocytic. There is evidence to show that from two hours to four hours after inoculation either the finely

granular polynuclear cell *or* the coarsely granular polynuclear cell may be the principal phagocyte. (See experiments 20 and 20 A and also 21 with 21 A.)

In experiment 19 (one hour) the finely granular polynuclear cell was the chief phagocyte, viz. 58 per cent., and 284 proved phagocytic. Agglutination of these cells was noted after one hour and also after four hours.

*The coarsely granular eosinophile cells.*—In every experiment with the *B. coli* these cells were proved to be phagocytic. In experiment 18 (fifteen minutes) they amounted to 76 per cent. and sixteen were phagocytic. In experiments 20 A (two hours) and 21 A (four hours) the coarsely granular polynuclear cells were 82 per cent. and 71 per cent., with 208 and 246 phagocytic respectively out of 500 cells. These cells showed the greatest phagocytic activity after fifteen minutes, two hours (experiment 20 A) and four hours (experiment 21 A).

*The mononuclear cells.*—In every instance these cells were phagocytic, but only to a very moderate degree, and as the intervals after inoculation were increased these cells tended to diminish in number. In experiment 19 (one hour) they amounted to 41 per cent. with 33 phagocytic, while in experiment 22 (eight hours), which proved rather an exception to the rule, they were 14 per cent. and 22 phagocytic.

*The omentum.*—No change of importance was noted.

*The bone-marrow.*—No bacilli were seen in any of the films. Nucleated red cells were noted during the counts in the following experiments, 19 (one hour), 20 (two hours), 21 (four hours); also in experiment 19 polychromatophilic degeneration was found.

The non-granular mononuclear type of cell averaged 50 per cent. in experiments 18 (fifteen minutes), 19 (one hour), and 21 (four hours). There was also a corresponding increase in the granular myelocyte.

In experiments 20 (two hours) and 23 (seventeen hours) the mononuclear type amounted to 79 per cent. and 84 per cent. respectively, accompanied by a marked decrease in the granular cells.

*Summary of experiments with cultures of the bacillus pyocyaneus.*

*The blood. Total number of leucocytes per c.mm.*—In five cases there was found to be a pathological leucocytosis. It was only slight, however, except in the twenty-four-hours case, in which it amounted to 3,000 per c.mm. In the quarter-hour experiment the leucocytes were quantitatively the same before and after inoculation.

*Differential leucocyte count.*—There was an absolute and relative increase of the *finely granular polynuclear cells* in every instance. The greatest increase in the relative numbers occurred in the two-hours case (84·2 per cent. as against 52·2 per cent.) and there were 2,598 more of these leucocytes in the pathological blood in the six-hours experiment than in the physiological.

An absolute and relative increase in the number of the *coarsely granular eosinophiles* was found in the quarter-hour and the one-hour cases, but *otherwise* there was a diminution in every other instance.

In one example a large number of transitional leucocytes were present in the physiological blood (5·4 per cent.), while this number was reduced to one fifth in the pathological blood.

No constant changes were found in the mononuclear cells in any of these experiments.

*In the six-hours case six of the finely granular polynuclear cells in the blood contained numerous bacilli.* The cells were very much degenerated.

*The erythrocytes.*—No abnormal changes were noted in the red cells in any of these experiments.

*The peritoneal exudate.*—In nearly every instance it was abundant and in the last three experiments it was turbid. Large numbers of phagocytes were seen without exception, and in the latest cases they were very numerous. All the signs of diffuse peritonitis were observed in the twenty-four-hours case.

*The great omentum.*—In the last experiment the twenty-four-hours case, the surface of the omentum was covered with flakes of lymph and pus, and it was retracted towards the diaphragm. It was also very vascular. Enormous masses of the finely granular polynuclear cells, mostly degenerated, were seen in film preparations of the exudate from the surface and large numbers of micro-organisms, both intra and extra-cellular.

*The cells.—The coarsely granular eosinophiles* were found to be important phagocytes in the one- and two-hours experiments. In the former case they amounted to 37·4 per cent. out of 500 cells and 148 were definitely phagocytic, whilst in the latter instance they amounted to 41·2 per cent. out of 500 cells and 199 were phagocytic. In the other cases they were present in very small numbers, and in the last instance, the twenty-four-hours case, none were seen.

*The small mononuclear cells* totalled 97·4 per cent. out of 500 cells in the fifteen-minutes experiment, but only three were phagocytic, whilst 28·6 per cent. out of 500 cells were recorded in the one-hour case, of which eleven were phagocytic. The large mononuclear cells amounted to 15·8 per cent. out of 500 cells in the last experiment, but none were phagocytic.

*The finely granular polynuclear cells* were the chief phagocytes in the last three experiments, whilst in the one- and two-hour cases they were found to be very numerous. In the eight-hours experiment no less than 80·8 per cent. were counted in the peritoneal exudate, of which every cell was proved to be phagocytic. In the last case, although 385 of these cells were found, out of 500 none contained bacilli (see "Great Omentum").

*The bacilli.*—In most instances the bacilli showed the usual appearances of capsular formation, and some bacilli, especially those in the interior of the phagocytes, were beaded or gave evidence of polar staining. Agglutination in all cases was very slight.

*The bone-marrow.*—It is most unfortunate that so many of the bone-marrows of these animals had to be cancelled because the specimens were not satisfactory. In the two examples in which the marrow was examined, the two-hours and twenty-four-hours cases, a very marked difference in the percentage of the small and large non-granular mononuclear cells was found. In the former instance the percentage total of these cells amounted to 47·5 per cent. and in the latter instance to 75·4 per cent. The increase in the non-granular cells was chiefly at the expense of the neutrophilic and eosinophilic myelocytes. The finely granular polynuclear cells amounted to 2·5 per cent. in the former case, while none were seen in the latter. No bacilli were found in either marrow. No mitotic figures were seen. Only one normoblast was observed in the two-hours marrow and four of these cells in the twenty-four-hours marrow.

*Summary of experiments with the bacillus coli and opium.*

*The blood. The total number of leucocytes per c.mm.*—The feature of the counts in this series was their marked variability. The following three experiments showed increase in the leucocytes of the pathological blood.

Experiment 59 (fifteen minutes): physiological blood 8,300, pathological blood 9,800. Experiment 62 (two hours): physiological blood 3,200, pathological blood 6,000. Experiment 63 (four hours): physiological blood 4,600, pathological blood 6,200. Thus a considerable leucocytosis occurred after two and four hours.

On the other hand, a decrease occurred in the remaining three.

Experiment 60 (thirty minutes): physiological blood 8,300, pathological blood 7,500. Experiment 61 (one hour): physiological blood 9,100, pathological blood 4,600. Experiment 64 (six hours): physiological blood 8,100, pathological blood 3,400; here the leucopenia was noticeable after one hour and six hours.

Possibly this variation may be accounted for by the susceptibility of the individual guinea-pig to the action of morphia. In experiment 61 (one hour) an extra large dose was accidentally administered, and here there was a marked leucopenia, but all the other animals received a uniform quantity.

*The differential leucocyte count.—The finely granular polynuclear cells* were absolutely increased in experiments 59 (fifteen minutes), 60 (thirty minutes), 62 (two hours), and 63 (four hours). In the first two cases this absolute increase was slight, in the last two very marked, *e. g.* experiment 63 (four hours), physiological blood 1,150 per c.mm. and pathological blood 3,410 per c.mm.

In experiment 61 (one hour with the large dose of opium) and experiment 64 (six hours) there was a large absolute decrease, with a relative increase in the finely granular polynuclear cells of the pathological blood.

*The coarsely granular polynuclear cells* were on the whole absolutely decreased in the pathological blood of this series. We may quote experiment 61 (one hour), where the number of these cells was 273 per c.mm. in the physiological blood as against 184 in the pathological blood, and also experiment 64 (six hours), where the coarsely granular polynuclear cells were reduced to 510 per c.mm. in the pathological blood (the number for the

physiological blood was 1053 per c.mm.). The largest decrease was in experiment 59 (fifteen minutes) when the physiological blood contained 249 per c.mm. and the pathological blood only 98. An exception was furnished by experiment 62 (two hours) in which the coarsely granular polynuclear cells were increased 2·5 : 1 in the pathological blood.

*The mononuclear cells* showed a large absolute increase in four experiments. After fifteen minutes (experiment 59) and two hours (experiment 62) there was only a moderate absolute increase. In experiment 61 (one hour), where the dose of opium was large, the mononuclear cells of the pathological blood dropped to 874 per c.mm. (physiological blood 3,639 per c.mm.).

*Mast-cells* were present in the physiological blood of four experiments, but only in small numbers. They were absent from the pathological blood in all cases.

*The red cells* showed no changes.

*The peritoneal exudate.*—On the whole the peritoneal fluid was abundant. A very constant phenomenon was the marked distension (with injection of peritoneal vessels) occurring in the stomach and intestinal coils; this was uniformly present in all instances. In the hanging drop preparations the cells were noted to be agglutinated and the bacilli numerous in experiment 64 (six hours), and the bacilli were also numerous in the exudate of experiment 61 (one hour).

*The finely granular polynuclear cell* was proved to be phagocytic in every experiment with the *B. coli* and opium after fifteen minutes. In experiment 59 (fifteen minutes) the coarsely granular polymorphonuclear cell was, as noted later, strongly phagocytic, but numerous endothelial cells (not included in the differential count) were present in addition, *all of which were phagocytic.* (See note on experiment 60 below.)

In experiments 61 (one hour), 62 (two hours), 64 (six hours) the finely granular polynuclear cells averaged 47 per cent. and 213 phagocytic.

The finely granular polynuclear cell was the predominant phagocyte in experiment 63 (four hours)—71 per cent., with 355 phagocytic.

In experiment 60 (thirty minutes) these cells numbered 1 per cent., with only four phagocytic. In this case the *rôle* of the coarsely granular polynuclear cells was taken by the endothelial

cells, which amounted to 86 per cent. while 145 were proved to be phagocytic.

In every case *the coarsely granular polymorphonuclear cell* was shown to be phagocytic. It was notably the important phagocyte after fifteen minutes (experiment 54), for here these cells numbered 73 per cent. with 155 phagocytic (in this case it was of interest that the endothelial cells were powerfully phagocytic). In this experiment the finely granular polymorphonuclear cells were non-phagocytic.

The coarsely granular polynuclear cell was also notably phagocytic after two hours (experiment 62)—40 per cent. and 176 phagocytic, and also after six hours (experiment 64)—41 per cent. with 162 phagocytic.

In these last two cases the phagocytic activity of both classes of polymorphonuclear cells was about equal.

After thirty minutes (experiment 60), when the endothelial phagocytosis was so marked, there was a great decrease in the numbers and phagocytic activity of the coarsely granular polynuclear cells (3 per cent., with only 12 phagocytic.)

Nothing of importance was noted as regards the mononuclear cells, except that in every instance they were seen to be slightly phagocytic.

*The omentum.*—Injection of the peritoneal vessels was a marked feature.

*The bone-marrow.*—In no case were any micro-organisms found in the films. Nucleated red cells were observed in every instance except after four hours (experiment 63). In experiment 60 (thirty minutes) thirty-seven normoblasts, thirty-three megaloblasts, eleven microblasts, and four gigantoblasts were seen while counting 1,000 cells.

In all the experiments after 59 (fifteen minutes) and 60 (thirty minutes) the mononuclear non-granular type of cell averaged 64 per cent.; thus it appears that this cell was the predominant one at the longer intervals after inoculation of the *B. coli* with opium. This increase was at the expense of the granular type of mono- and polynuclear cell.

In experiment 59 (fifteen minutes) and in experiment 60 (thirty minutes) the non-granular mononuclear cells only numbered 47 and 37 per cent. respectively, while the granular myelocytes were correspondingly increased.

*Summary of experiments with the bacillus aerogenes capsulatus.*

*The blood. Total number of leucocytes per c.mm.*—A pathological leucocytosis occurred in every instance but one—the one-hour case. In this example the number of leucocytes was similar in each instance. In the last three experiments the leucocytosis was marked. In the six-hours case the number of leucocytes in the pathological blood amounted to 8,400 more than in the physiological blood.

*Differential leucocyte count. The finely granular polynuclear cells* were increased both relatively and absolutely in every instance except in the one-hour experiment, in which they were diminished. The increase was in most instances excessive, especially in the six-hours experiment, in which these cells totalled 87 per cent. or 8,700 per c.mm. as against 33 per cent. or 528 per c.mm. in the physiological blood.

*The coarsely granular eosinophiles* were in most instances diminished both relatively and absolutely. In the two cases in which an increase occurred it was only very slight.

*The small mononuclear cells* were present in large numbers in both physiological and pathological blood in the first case, but these cells did not show any constant changes in these experiments.

*The erythrocytes.*—Three normoblasts were seen in the pathological blood in the six-hours case, otherwise no changes in the red cells were recorded.

*The peritoneal exudate.*—In five cut of the six cases the exudate was stated to be abundant. In the sixth example no fluid was seen. In one instance, the six-hours case, the exudate was turbid. In most examples only a few bacilli were seen.

*The great omentum.*—In the last four experiments the peritoneum was injected, and numerous flakes of lymph and pus were seen on the surface of the great omentum in the twenty-four-hours case. It was also very injected and retracted towards the diaphragm in this last example.

*The cells.—The coarsely granular eosinophiles* were only present in very small numbers in these experiments, and certainly did not play an important part in peritoneal phagocytosis.

*The small mononuclear cells* were present in large numbers in

the first case, but afterwards greatly diminished in numbers. They amounted to 99·6 per cent. out of 500 cells in the exudate of the quarter-hour guinea-pig, 33·2 per cent. in the one-hour, and 14·8 per cent. in the exudate of the two-hours animal. In these three cases there was complete absence of phagocytosis.

*The finely granular polynuclear cells,* although present in very large numbers from the one hour-experiment onwards, did not show much evidence of phagocytosis. In the six- and twenty-four hours guinea-pigs these cells totalled 92 per cent. and 90·2 per cent. respectively of the cells in the peritoneal exudate. In the case of the two-hours guinea-pig's peritoneal exudate 399 of these cells were found while counting 500, of which 161 were phagocytic.

*The bacilli.*—In no instance were the bacilli very numerous. In three cases in which they were intra-cellular many were degenerated. Some bacilli were vacuolated, others showed irregular staining, others beading, and many stained feebly, whilst the extra-cellular bacilli showed none of these appearances

Bacillary agglutination was absent.

*Phagocytosis in relation to the great omentum.*—Perhaps the most interesting phenomenon concerning these experiments was observed in the case of the twenty-four-hours guinea-pig. The finely granular polynuclear cells in the peritoneal exudate amounted to 90·2 per cent. out of 500 of which none were found to be phagocytic and no free bacilli were seen in the exudate. *Film preparations made from the surface of the great omentum showed 99·6 per cent. of the finely granular polynuclear cells out of* 500, *and every cell was phagocytic.* Large numbers of bacilli which were seen in the phagocytes gave evidence of degenerative changes.

*The bone-marrow.*—No constant alterations were observed in the bone-marrow in these experiments. In two cases the small and large non-granular mononuclear cells were over 70 per cent. of the cells, but these observations were inconstant. Micro-organisms were absent in every case as far as we could judge. No mitotic figures were observed; in two instances the nucleated red cells were numerous. In the one-hour example ten normoblasts were seen while counting 1,000 leucocytes, whilst in the six-hours experiment thirteen normoblasts and two megaloblasts were seen during a count of 1,000 white cells.

*Summary of experiments with dead cultures of the bacillus coli.*

*The blood. Total number of leucocytes per c.mm.*—In every case but one the number of leucocytes in the physiological blood was greater than in the pathological blood. The pathological leucopenia was marked; in one case it amounted to 3,100 per c.mm. In the twenty-four-hours experiment, however, the number of leucocytes in the pathological blood was greater than in the physiological by 2,400 per c.mm. The pathological leucopenia in these cases is of great interest and might be described as the negative phase.

*Differential leucocyte count.—The finely granular polynuclear cells* were diminished both absolutely and relatively in the pathological blood of the one- and two-hours guinea-pigs and absolutely only in the four- and six-hours animals. In the twenty-four-hours experiment a relative and absolute increase occurred in the pathological blood.

*The coarsely granular eosinophiles* showed a relative increase in the pathological blood in four out of the five cases and an absolute gain in three of these. In one instance the relative increase amounted to 7·26 per cent. and the absolute to 143. In the last example there was both an absolute and relative diminution of these cells in the pathological blood.

*The mononuclear cells* showed no important changes.

*The erythrocytes.*—No nucleated red cells or degenerative changes in the red cells were noticed in any of these experiments.

*The peritoneal exudate.*—This was described as abundant in four cases, in fair quantity and turbid in one, whilst none was seen in the last example. Agglutination of the leucocytes was observed in the peritoneal exudate in the three last experiments. No free bacilli were seen in the peritoneal fluid in the twenty-four-hours case.

*The great omentum.*—This was seen to be retracted in the last experiment.

*The cells.—The coarsely granular eosinophiles* were found in large numbers in the peritoneal exudate in the one- and two-hours guinea-pigs and to a less extent in the six-hours animal. In the two-hours experiment they amounted to 62 per cent. out of a total of 400 cells and 93 of these were phagocytic.

*The small mononuclear cells* amounted to 92·6 out of 500, and 10 of these were phagocytic, in the quarter-hour pig. In the one hour animal's peritoneal exudate these cells were found to be present to the extent of 97 out of 439, but none were phagocytic.

*The finely granular polynuclear cells* were the chief phagocytes in the one-, four-, six-, and twenty-four-hours animals' peritoneal exudate. In the last of these experiments they formed 97·6 per cent. out of a total of 500, but none were phagocytic. In fact, the phagocytic properties of these cells in these experiments were very slight. In the six-hours guinea-pig sixteen cells were phagocytic out of 361, and this was the best example.

In one instance many free bacilli were seen which were mostly vacuolated, but this was the only example in which they occurred.

*The bone-marrow.*—The non-granular mononuclear cells were the predominant type in the bone-marrow in all cases but two, the one- and four-hours animals. In these instances the non-granular mononuclear cells were under 60 per cent. of all the cells, while in the other cases they were over 70 per cent. In one example the non-granular cells were diminished at the expense of the polymorphonuclear cells and in the other at that of the neutrophilic myelocytes.

*The erythrocytes.*—Nucleated red cells were numerous in the last four experiments.

In the two-hours guinea-pig three megaloblasts and nine normoblasts were seen while counting 1,000 leucocytes; in the four-hours guinea-pig three megaloblasts and four normoblasts were seen while counting 1,000 leucocytes; in the six-hours guinea-pig six megaloblasts and three normoblasts were seen while counting 1,000 leucocytes; in the twenty-four-hours guinea-pig one megaloblast and fifteen normoblasts were seen while counting 1,000 leucocytes.

No micro-organisms were seen in any of these experiments and no mitotic figures.

### *Summary of experiments with the bacillus typhosus.*

*The blood. Total number of leucocytes per c.mm.*—In five instances there was a pathological leucocytosis. In the case of the four-hours guinea-pig (38 A) a very slight diminution

occurred. The most marked leucocytosis was observed in the pathological blood of the seventeen-hours animal, an excess of 5,700 per c.mm.

*Differential leucocyte count.*—In every one of the six guinea-pigs an absolute increase in the number of the *finely granular polynuclear cells* was found in the pathological blood. In the quarter-hour and one-hour experiment there was no relative increase in the number of these cells in the pathological blood. The most marked relative and absolute increase occurred in the pathological blood of the seventeen-hours animal, a relative gain of 37·2 per cent and an absolute gain of 5,947 per c.mm.

There was no relative increase in the number of *the coarsely granular eosinophiles* in the pathological blood in any of these experiments, whilst in the blood of the seventeen-hours guinea-pig none were seen, although 138 of these cells had been counted per c.mm. in the physiological blood. *The mononuclear cells* presented no constant changes.

*The erythrocytes.*—One normoblast was seen while counting 500 white cells in the pathological blood of the quarter-hour experiment, but otherwise no nucleated red cells were seen. Polychromatophilia was present in the pathological blood of experiment 38 A.

*The peritoneal exudate.*—In all cases, but one, the peritoneal exudate was either abundant or in fair quantity. The exudate was turbid in the last four experiments and the intestines were injected. No true pus was seen.

*The great omentum* was retracted towards the diaphragm and injected in the seventeen-hours guinea-pig.

*The cells.*—*The coarsely granular eosinophiles* failed to play an important part in peritoneal phagocytosis in any of these experiments.

*The small mononuclear cell* appeared to be a phagocyte of the utmost importance. It formed 90 per cent. of the cells in the peritoneal exudate of the quarter-hour guinea-pig, 41·6 per cent. in the one-hour, 13·2 per cent. in the two-hours, 24·8 per cent. in the four-hours, and 27·2 per cent. in the six-hours experiment, and in the one-hour example 13 out of a total of 208 of these cells were phagocytic.

*The finely granular polynuclear cell* from the one-hour experiment onwards was, however, the most important phagocyte. In

the case of the seventeen-hours animal no less than 97·8 per cent. of these cells were seen in the peritoneal exudate. True phagocytosis was not well shown in any of the experiments, but degenerative changes in these cells were frequently observed in the latest cases.

Phagocytic agglutination was of common occurrence.

*The bone-marrow.*—A distinct increase in the small and large non-granular mononuclear cells was observed in the last four experiments, especially in the case of the six-hours. No other constant changes were seen in the remaining varieties of marrow leucocytes. No mitotic figures were present. No bacteria were found in any of the specimens.

In one instance, only, nucleated red cells were abundant. In the case of the four-hours guinea-pig two normoblasts were seen while counting 1,000 leucocytes, but in the one-hour animal eleven megaloblasts and six normoblasts were seen while counting 500 white cells.

*Summary of experiments with the staphylococcus pyogenes aureus.*

*The blood. Total number of leucocytes per c.mm.*—In every instance the pathological blood showed a leucocytosis. In the first two experiments, 47 (fifteen minutes) and 48 (one hour), this was slight. But the leucocytosis was marked in the last four experiments, with the exception of experiment 50 (four hours), where the pathological count was only 4,200 per c.mm. against the physiological count of 3,100 per c.mm. The lowest count was that of experiment 47 (fifteen minutes,) physiological blood 1,500 per c.mm. and pathological blood 1,600 per c.mm., while the highest was that of experiment 52 (eighteen hours), physiological blood 3,400 per c.mm. and pathological blood 10,700 per c.mm.

*The differential leucocyte count.*—In every case the *finely granular polynuclear cells* showed both a relative and an absolute increase. This was hardly noticeable in experiment 47 (fifteen minutes), but was quite well marked in all the others. This progressive increase, however, was not so marked in experiment 50 (four hours) and experiment 51 (seven hours), as the ratio of increase of these cells per c. mm. in the pathological blood as compared with the physiological blood was about 2 : 1 and 2·5 : 1

respectively. The highest figures were those of experiment 52 (eighteen hours). In the physiological blood the finely granular polynuclear cells were 51·8 per cent. and 1,734 per c.mm. and in the pathological blood 57·2 per cent. and 6,099 per c.mm.

*The coarsely granular eosinophile cells* showed some relative and absolute increase in the pathological blood of experiments 47 and 48 (fifteen minutes and one hour). Also in the pathological blood of experiment 50 (four hours) they were present in very small numbers (only 8 per c.mm.) and absent from the physiological blood. In the remaining three experiments these cells showed a relative and absolute diminution; and though present in the pathological blood of experiment 49 (two hours) in small numbers, they were totally absent from the pathological blood of experiments 51 (seven hours) and 52 (eighteen hours). The coarsely granular eosinophile cells were never present in large numbers (the highest count was 2·4 per cent. and 70 per c.mm. in the physiological blood of experiment 49 (two hours), and they appeared to diminish the longer the interval after the inoculation of the staphylococcus pyogenes aureus.

*The mononuclear cells.*—Taking the small lymphocytes and the large lymphocytes together, the most noteworthy feature was a slight relative diminution and at the same time a moderate absolute increase in the number of these cells present in the pathological blood.

The only exception occurred in experiment 50 (four hours) where in the physiological blood the percentage of mononuclears was 39 and the number per c.mm. 1,178, while in the pathological blood the percentage was only 7 and the number per c. mm. 294.

*Note.*—The large absolute increase in the mononuclears seen in experiment 52 (eighteen hours) is accounted for by the big leucocytosis (1,496 per c.mm. in the physiological blood and 4,066 in the pathological blood).

No constant change was observed in the case of the large hyaline cells. Mast-cells were entirely absent in five experiments and only present in small numbers in the physiological blood of the remaining one.

*The red cells* showed no change.

*The peritoneal exudate.*—On the whole this was abundant except in the eighteen-hours experiment (No. 52). In the hanging drop preparations the cocci appeared to be inside the cells in two

cases (after two hours and seven hours). Numerous extracellular cocci were seen. The important phagocyte appears to be the finely granular polynuclear cell, which in experiment 52 (eighteen hours) numbered 92 per cent. and 151 were proved phagocytic. The longer the interval after inoculation the more marked was the phagocytic action of the finely granular polynuclear cells. In experiment 47 (fifteen minutes) this cell is hardly in evidence at all as a phagocyte (4 per cent. and 6 phagocytic), while the number of mononuclears was 91·6 per cent.

The coarsely granular eosinophile cells in no case exceeded 10 per cent. (experiment 47, fifteen minutes), but notwithstanding this, a fair number were proved to be phagocytic in the first four experiments.

The mononuclear cells were numerous in experiments 47 (15 minutes) and 48 (one hour), being 94 and 73 per cent. respectively, and from this point rapidly diminished in numbers. These cells were proved to be phagocytic, but their importance as such was insignificant. They were present to the number of 94 per cent. in experiment 47 (fifteen minutes) and 24 were proved phagocytic.

*The great omentum* showed no marked changes.

*The bone-marrow.*—In no instance were any cocci seen in the films. In two cases (experiment 47, fifteen minutes, and experiment 49, two hours) nucleated red cells were observed. In the first four experiments (47–50) the non-granular mononuclear cells averaged 67 per cent.; in the last two experiments, when the interval after inoculation was seven hours and eighteen hours, these cells dropped to 48 per cent.; this deficit was mainly made up by an increase in the various types of the granular myelocytes. In experiment 52 (eighteen hours) the finely granular polynuclear cells amounted to 12 per cent.

*Summary of experiments with the staphylococcus albus.*

*The blood. Total number of leucocytes per c.mm.*—In every case the number of leucocytes per c.mm. was increased in the pathological blood. This increase advanced steadily the longer the interval after the inoculation of the *staphylococcus albus*. In experiment 1 (fifteen minutes) the physiological blood contained 7,200 leucocytes per c.mm. and the pathological blood

8,700; while in experiment 5 (six hours) the numbers were 3,000 per c.mm. (physiological blood) against 11,000 (pathological blood).

*The differential count.*—In each instance the *finely granular polynuclear cells* were both relatively and absolutely increased. This increase became very marked in the experiments after one hour, for in experiment 3 (two hours) these cells amounted to 57 per cent. and 5,301 per c.mm. in the physiological blood as against 80 per cent. and 10,080 per c.mm. in the pathological blood. The greatest absolute increase occurred in experiment 5 (six hours), in which the finely granular polynuclear cells numbered 1290 per c.mm. in the physiological blood, as against 7,260 per c.mm. in the pathological blood.

*The coarsely granular eosinophile cells* were practically stationary as regards relative increase in the pathological blood of experiments 1 (fifteen minutes) and 2 (one hour); but they were absolutely increased in the pathological blood after fifteen minutes in the proportion of 3 : 2 per c.mm. (432 per c.mm. in the physiological blood, against 609 per c.mm. in the pathological blood). There was a very slight absolute increase also in the pathological blood of experiment 2 (one hour). In the remaining three experiments the coarsely granular eosinophile cells were both absolutely and relatively decreased in the pathological blood. This was notably the case in experiments 3 (two hours) and 4 (four hours); *e. g.* in experiment 4 the coarsely granular eosinophile cells amounted to 10 per cent. and 700 per c.mm. in the physiological blood, as against 0·6 per cent. and only 84 per c.mm. in the pathological blood.

*The mononuclear cells* exhibited no important changes; their large absolute increase in the pathological blood of experiment 5 (six hours) is accounted for by the leucocytosis, as at the same time there was a relative decrease in the number of these cells. In the experiment above referred to the mononuclears numbered 32 per cent. and 960 per c.mm. in the physiological blood, as against 19 per cent. and 2,090 per c.mm. in the pathological blood.

*The mast-cells* were absolutely increased in the pathological blood of experiment 2 (one hour) and of experiment 5 (six hours). No change of importance was noted in the *red cells.*

*The peritoneal exudate.*—This was in all cases abundant and

the cells were very numerous. In the hanging drop preparations not many free cocci were seen.

The *finely granular polynuclear cells* were proved to be phagocytic in all the experiments except the first (fifteen minutes); in this instance and also in experiment 2 (one hour) the number of these cells was almost negligible. In the remaining three experiments (two hours, four hours, six hours) the percentage of the finely granular polynuclear cells was high—*e. g.* in experiment 4 (four hours) 85 per cent.

The phagocytic activity of these cells was in no instance great; in experiment 2 (one hour) they amounted to 11 per cent. with 54 containing cocci, which was the greatest number proved to be phagocytic in the whole series. In experiment 5 (six hours) the finely granular polynuclear cells amounted to 91 per cent., but micro-organisms were observed to be intra-cellular in only 37 instances.

The *coarsely granular eosinophile cells* were found to contain cocci in every experiment. These cells were present in very small numbers in all the experiments (except 1 A, to be shortly referred to). The highest count was in experiment 3 (two hours), where they amounted to 16 per cent. At the same time the phagocytic activity of the coarsely granular eosinophile cell was a feature of this series. In experiment 2 (one hour) they numbered 2·4 per cent. with 10 phagocytic, and in experiment 4 (4 hours) they amounted to 6·4 per cent with 24 phagocytic.

Experiment 1 A, which we include, has already been referred to by Dudgeon and Sargent in their work on the bacteriology of peritonitis. It was to a certain extent unique, for after an interval of only fifteen minutes from the time of inoculation with the *staphylococcus albus*, the coarsely granular eosinophile cells numbered 54 per cent. with 131 phagocytic, many of the cells containing several cocci.

The *mononuclear cells* proved to be slightly phagocytic after one hour (experiment 2), four hours (experiment 4), and six hours (experiment 5). In experiment 1 (fifteen minutes) and in experiment 2 (one hour) these cells numbered 98 and 87 per cent. respectively. In all the remaining examples their numbers fell in proportion to the preponderance of the finely granular polynuclear cells.

*The omentum.*—No important changes were noted.

*The bone-marrow.*—In no instance were any cocci detected in the films. In all cases a few normoblasts and twice megaloblasts were seen while making the differential count. The following table of percentages will show that there was little alteration in the number of the mononuclear non-granular cells present after inoculation with the *staphylococcus albus.*

| | | | |
|---|---|---|---|
| Experiment | 1 | 15 minutes | 57 per cent. |
| „ | 2 | 1 hour | 56 „ |
| „ | 3 | 2 hours | 61 „ |
| „ | 4 | 4 „ | 51 „ |
| „ | 5 | 5 „ | 62 „ |

An exception was made in the case of experiment 4, which shows a difference of 10 per cent.

The neutrophile myelocyte varied from 25 to 35 per cent.

*Summary of experiments with the streptococcus pyogenes.*

*The blood. Total number of leucocytes per c.mm.*—In every experiment the number of leucocytes per c.mm. in the pathological blood was increased. In most cases this leucocytosis was only moderate. The highest count was obtained after four hours (experiment 74), where the figures were 1,300 per c.mm. for the physiological blood against 3,200 in the pathological blood.

*The differential count.*—In every instance there was both a relative and an absolute increase of the *finely granular polymorphonuclear cells* in the pathological blood. This was not very marked until experiment 74 (four hours), when these cells amounted to 44 per cent. and 572 per c.mm. in the physiological blood as against 91 per cent. with 2,912 per c.mm. in the pathological blood. A similar large increase occurred after six hours and after twenty-four hours, only it was not so great as in the four-hours experiment.

*The coarsely granular polymorphonuclear cells* were absolutely and relatively decreased in every instance in the pathological blood except after fifteen minutes (experiment 71), when they were absent from the physiological blood and numbered 0·2 per cent. and 3 per c.mm. in the pathological blood. The diminution of these cells was most marked after one hour; here they amounted to 3 per cent. and 84 per c.mm. in the physiological

blood as against 0·2 per cent. with 6 per c.mm. in the pathological blood. The coarsely granular polymorphonuclear cells were in no instance numerous.

In all cases (except after fifteen minutes and one hour, when there was a very slight increase) *the mononuclear cells* were relatively and absolutely diminished in the pathological blood; *e. g.* after six hours (experiment 75) they numbered 36 per cent. and 1610 per c.mm. in the physiological blood as against 14 per cent. and 686 per c.mm. in the pathological blood.

*The finely basophilic cells* showed an increase in the earlier experiments and a decrease in the later.

*The red cells.*—Polychromatophilia was well marked after one hour (experiment 72), when one normoblast was seen while counting 500 leucocytes, and also after four hours (experiment 74).

*The peritoneal exudate* was abundant after one hour, two hours, and four hours. None was obtained after fifteen minutes and twenty-four hours and very little after six hours. In nearly every instance both the visceral and parietal peritoneum was noted to be reddened and injected. On the whole, cells were numerous, but not agglutinated. Cocci were very abundant after one hour.

After fifteen minutes (experiment 71) the endothelial cells amounted to 91 per cent., but the *finely granular polynuclear cells* were entirely *absent*. In all the other experiments the percentage of these cells was very high. The lowest count occurred after two hours (experiment 73), when the finely granular polynuclear cells were 79 per cent. and the greatest after one hour (experiment 72), when these cells amounted to 97 per cent. *There was an entire absence of true phagocytosis on the part of these cells.*

*The coarsely granular polynuclear cells* were in no instance found to be phagocytic. They were absent in the exudate except in experiment 71 (fifteen minutes), where 1 per cent. were found, and in experiment 74 (six hours), in which case they only amounted to 0·4 per cent.

The *mononuclear cells* were never phagocytic and only present in extremely small numbers. The highest count was after two hours (experiment 73), when they amounted to 24 per cent., and in many cases these cells were as low as 3 or 4 per cent.

*The omentum.*—The vessels were much dilated and the peritoneum was markedly injected. No pus or flakes of lymph were seen. After fifteen minutes (experiment 71) the peritoneum appeared normal.

*The bone-marrow.*—In no case were any cocci seen in the films. In every instance nucleated red cells were present in far greater numbers than in any of the other series of this research. Not only were normoblasts and megaloblasts present in every case, but very often numbers of gigantoblasts were also seen.

After one hour (experiment 72) 160 normoblasts, 118 megaloblasts, and 59 gigantoblasts were found while counting 1,000 cells; also after four hours (experiment 74) 174 normoblasts, 55 megaloblasts, and 7 gigantoblasts were noted while counting the same number of leucocytes.

In all the experiments the non-granular mononuclear type of cell averaged 68 per cent. The lowest count occurred after twenty-four hours (experiment 76) and the highest after four hours (experiment 74), the percentages being 62 and 78 respectively.

In most cases the granular myelocytes averaged from 20 to 25 per cent.

*Summary of experiments with the pneumococcus.*

*The blood. The total number of leucocytes per c.mm.*—In every case the leucocytes were increased in the pathological blood, except after two hours (experiment 43), when they were stationary. This pathological increase was as a rule only moderate; *e. g.* in experiment 46 (forty hours) there were 3,100 leucocytes in the physiological blood and 3,500 in the pathological blood. The highest count was obtained in experiment 44 (four hours); here the physiological blood contained 2,600 per c.mm. against the pathological blood with 3,600 per c.mm.

*The differential count.*—In every instance *the finely granular polynuclear cells* showed both a relative and an absolute increase in the pathological blood. As a rule this increase was very marked. In experiment 44 (four hours) the figures were 38 per cent. and 988 per c.mm. in the physiological blood against 60 per cent. with 2,160 per c.mm. in the pathological blood. In the pathological blood of the six-hours animal six of these cells were seen to contain diplococci and many were degenerated.

*The coarsely granular polynuclear cells* were both relatively and absolutely increased in the pathological blood after fifteen

minutes (experiment 41) and after one hour (experiment 42); these cells were absolutely increased in the remaining experiments except in experiment 46 (40 hours), when they were entirely absent from the pathological blood. The largest absolute increase occurred after fifteen minutes (experiment 41), in the physiological blood the coarsely granular polynuclear cells here amounted to 1 per cent. and 35 per c.mm. against 3 per cent. and 132 per c.mm. in the pathological blood. In most instances the absolute increase was well marked.

In every case the *mononuclear cells* were both relatively and absolutely decreased in the pathological blood. This decrease was very marked after six hours (experiment 45) and after forty hours (experiment 46), *e. g.* in the physiological blood of experiment 46 these cells numbered 47 per cent. and 1,457 per c.mm. against 19 per cent. with 595 per c.mm. in the pathological blood.

The number per c.mm. of the finely granular basophilic cells showed a tendency to be increased in the pathological blood; but this was not constant (see experiments 43 and 45).

*The red cells* of the pathological blood often gave evidence of polychromatophilia. After forty hours (experiment 46) 8 normoblasts were seen while counting 500 cells in the pathological blood.

*The peritoneal exudate.*—On the whole this was scanty. After fifteen minutes (experiment 41) it was abundant. In the hanging drop preparations the condition of the cells was good, although with the exception of experiment 41 (fifteen minutes) they were not as a rule numerous. After forty hours (experiment 46) a very different picture was presented, as all the cells were too degenerated to make an accurate count possible. In experiment 45 (six hours) the cells were in excellent condition. Free cocci were present in many cases and were numerous after two hours (experiment 43) and four hours (experiment 44).

The finely granular polynuclear cells in every example of this series with the exception of experiment 41 numbered between 80 and 95 per cent. of the cells present. In experiment 41 (fifteen minutes) endothelial cells were present to the extent of 70 per cent.

In spite of this high percentage of the finely granular polynuclear cells practically no phagocytic activity was observed. Only a single cell was seen to be phagocytic in experiment 43

(two hours), when the finely granular polynuclear cells numbered 84 per cent. Very occasionally an endothelial cell was proved to be phagocytic, but these in no way supplied the place of the other cells in this respect.

The same remark applies to *the coarsely granular polynuclear cells* of this series as regards phagocytic activity. Only two cells (one after two hours, experiment 43, and the other after six hours, experiment 45) were proved to be phagocytic. These cells were also present only in very small numbers. The highest count was 16 per cent., in experiment 42 (one hour).

*The mononuclear cells* were never above 13 per cent. and only one cell was proved phagocytic in experiment 42 (one hour.)

*The omentum* showed no marked changes.

*The bone-marrow.*—In no instance were cocci seen in any of the films. With one exception (experiment 45, six hours) *nucleated red cells* were uniformly present and in much larger numbers than is the case with guinea-pigs' marrow; *e. g.* after two hours (experiment 43) 118 normoblasts and 63 megaloblasts were seen while counting 1000 cells.

With the exception of experiment 41 (fifteen minutes) the most important cell was the non-granular mononuclear variety. These cells numbered just over 70 per cent. in experiment 42 (one hour) and in experiment 43 (two hours). In the remaining three experiments, when the longer intervals of time were employed, they amounted to over 80 per cent. The granular myelocytes were correspondingly decreased, except in the case of experiment 41 (fifteen minutes); but this was not so noticeable in the last two experiments (six hours and forty hours), where the granular type of cell formed a large portion of the remaining 20 per cent.

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## TABULAR SYNOPSIS OF EXPERIMENTS.

### Staphylococcus albus.

EXPERIMENT 1.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the staphylococcus albus.*

| **The blood.** | *Physiological blood.* Leucocytes=7·200 per c.mm. | | | *Pathological blood.* Leucocytes=8·700 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 268 | 53·6 | 3888 | 282 | 56·4 | 4872 |
| Coarsely granular polynuclear cells | 32 | 6·4 | 432 | 36 | 7·2 | 609 |
| Small lymphocytes | 187 | 37·4 | 2664 | 157 | 31·4 | 2697 |
| Large lymphocytes | 7 | 1·4 | 72 | 2 | 0·4 | 34·8 |
| Large hyaline cells | 5 | 1·0 | 72 | 9 | 1·8 | 156·6 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 1 | 0·2 | 14·4 | 14 | 2·8 | 243·6 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was present in large amount.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 4 | 0·8 | — |
| Coarsely granular polynuclear cells | 7 | 1·4 | 3 |
| Small mononuclear cells | 481 | 96·2 | — |
| Large mononuclear cells | 7 | 1·4 | — |
| Transitional cells | 1 | 0·2 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 88 | 8·8 | |
| Neutrophilic myelocytes with typical nucleus | 181 | 18·1 | |
| Eosinophilic myelocytes with typical nucleus | 69 | 6·9 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 16 | 1·6 | |
| Finely granular polynuclear cells | 30 | 3·0 | |
| Coarsely granular polynuclear cells | 2 | 0·2 | |
| Small mononuclear cells | 450 | 45·0 | 57·2 |
| Large mononuclear cells | 122 | 12·2 | |
| Large hyaline cells | 22 | 2·2 | |
| Coarsely granular basophilic cells | 16 | 1·6 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | 4 | 0·4 | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Five normoblasts seen while counting 1000 leucocytes.

EXPERIMENT 1A.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the staphylococcus albus.*

**Peritoneal fluid.** This was clear and very abundant. The leucocytes were very numerous and appeared to be crowded with cocci.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 8 | 2 |
| *Coarsely granular polynuclear cells.* | *214* | *53·50* |
| Small mononuclear cells. | 103 | 25·75 |
| Large mononuclear cells | 75 | 18·75 |
| Transitional cells | — | — |
| | 400 | |

No less than 131 of the coarsely granular cells were phagocytic, while many of these cells contained numerous cocci.

The blood and bone-marrow were not examined in this experiment.

EXPERIMENT 2.—*Guinea-pig killed one hour after an intra-peritoneal injection of the staphylococcus albus.*

**The blood.**

| | *Physiological blood.* Leucocytes=5600 per c.mm. | | | *Pathological blood.* Leucocytes=6800 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 166 | 33·2 | 1848 | 250 | 50·0 | 3400 |
| Coarsely granular polynuclear cells | 28 | 5·6 | 336 | 14 | 4·8 | 340 |
| Small lymphocytes | 57 | 11·4 | 616 | 97 | 19·4 | 1292 |
| Large lymphocytes | 33 | 6·6 | 392 | 22 | 4·4 | 272 |
| Large hyaline cells | 211 | 42·2 | 2352 | 104 | 20·8 | 1360 |
| Mast cells | 1 | 0·2 | 12·2 | 3 | 0·6 | 40·8 |
| Transitional cells | 4 | 0·8 | 44·8 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was found to be abundant. Cells were numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 54 | 10·8 | 54 |
| Coarsely granular polynuclear cells | 12 | 2·4 | 10 |
| Small mononuclear cells | 432 | 86·4 | 15 |
| Large mononuclear cells | 2 | 0·4 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 32 | 3·2 | |
| Neutrophilic myelocytes with typical nucleus | 211 | 21·1 | |
| Eosinophilic myelocytes with typical nucleus | 77 | 7·7 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 8 | 0·8 | |
| Finely granular polynuclear cells | 12 | 1·2 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 420 | 42·0 | 56·1 |
| Large mononuclear cells | 141 | 14·1 | |
| Large hyaline cells | 52 | 5·2 | |
| Coarsely granular basophilic cells | 31 | 3·1 | |
| Finely granular basophilic cells | 1 | 0·1 | |
| Giant cells | 14 | 1·4 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Three normoblasts and five megaloblasts seen while counting 1000 white cells.

EXPERIMENT 3.—*Guinea-pig killed two hours after an intra-peritoneal injection of the staphylococcus albus.*

| **The blood.** | *Physiological blood.* Leucocytes = 9300 per c.mm. | | | *Pathological blood.* Leucocytes = 12,600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 287 | 57·4 | 5301 | 400 | 80·0 | 10080 |
| Coarsely granular polynuclear cells | 62 | 12·4 | 1116 | 13 | 2·6 | 378 |
| Small lymphocytes | 50 | 10·0 | 930 | 24 | 4·8 | 630 |
| Large lymphocytes | 27 | 5·4 | 465 | 11 | 2·2 | 252 |
| Large hyaline cells | 72 | 14·4 | 1302 | 48 | 9·6 | 1260 |
| Mast cells | 2 | 0·4 | 37·2 | 1 | 0·2 | 25·2 |
| Transitional cells | — | — | — | 3 | 0·6 | 75·6 |
| | 500 | | | 500 | | |

**Blood platelets** appeared to be very numerous.

**Peritoneal fluid.** This was found to be abundant. Cells were very numerous and a few free cocci seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 340 | 68·0 | 34 |
| Coarsely granular polynuclear cells | 78 | 15·6 | 44 |
| Small mononuclear cells | 76 | 15·2 | — |
| Large mononuclear cells | 6 | 1·2 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 40 | 4·0 | |
| Neutrophilic myelocytes with typical nucleus | 179 | 17·9 | |
| Eosinophilic myelocytes with typical nucleus | 109 | 10·9 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 11 | 1·1 | |
| Finely granular polynuclear cells | 7 | 0·7 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 489 | 48·9 | 61·3 |
| Large mononuclear cells | 124 | 12·4 | |
| Large hyaline cells | 18 | 1·8 | |
| Coarsely granular basophilic cells | 8 | 0·8 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 12 | 1·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | 2 | 0·2 | |
| | 1000 | | |

Four normoblasts seen while counting 1000 leucocytes.

EXPERIMENT 4.—*Guinea-pig killed four hours after an intraperitoneal injection of the staphylococcus albus.*

| **The blood.** | *Physiological blood.* Leucocytes=7000 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes=14,000 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 214 | 42·8 | 3010 | 410 | 82 0 | 11480 |
| Coarsely granular polynuclear cells | 50 | 10·0 | 700 | 3 | 0·6 | 84 |
| Small lymphocytes | 211 | 42·2 | 2940 | 69 | 13·8 | 1960 |
| Large lymphocytes | 12 | 2·4 | 140 | 4 | 0·8 | 112 |
| Large hyaline cells | 5 | 1·0 | 70 | 6 | 1·2 | 140 |
| Mast cells | 4 | 0·8 | 56 | — | — | — |
| Transitional cells | 4 | 0·8 | 56 | 8 | 1·6 | 280 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was very abundant. Cells were numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 426 | 85·2 | 9 |
| Coarsely granular polynuclear cells | 32 | 6·4 | 24 |
| Small mononuclear cells | 27 | 5·4 | 10 |
| Large mononuclear cells | 15 | 3·0 | 5 |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 69 | 6·9 | |
| Neutrophilic myelocytes with typical nucleus | 124 | 12·4 | |
| Eosinophilic myelocytes with typical nucleus | 95 | 9·5 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 59 | 5·9 | |
| Finely granular polynuclear cells | 52 | 5·2 | |
| Coarsely granular polynuclear cells | 11 | 1·1 | |
| Small mononuclear cells | 401 | 40·1 | 51·4 |
| Large mononuclear cells | 113 | 11·3 | |
| Large hyaline cells | 45 | 4·5 | |
| Coarsely granular basophilic cells | 14 | 1·4 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 14 | 1·4 | |
| Transitional cells | 2 | 0·2 | |
| Amphophilic cells | 1 | 0·1 | |
| | 1000 | | |

Fourteen normoblasts and three megaloblasts seen while counting 1000 white cells.

EXPERIMENT 5.—*Guinea-pig killed six hours after an intra-peritoneal injection of the staphylococcus albus.*

| **The blood.** | *Physiological blood.* Leucocytes=3000 per c.mm. | | | *Pathological blood.* Leucocytes=11,000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 213 | 42·6 | 1290 | 331 | 66·2 | 7260 |
| Coarsely granular polynuclear cells | 110 | 22·0 | 660 | 27 | 5·4 | 550 |
| Small lymphocytes | 156 | 31·2 | 930 | 10 | 2·0 | 220 |
| Large lymphocytes | 5 | 1·0 | 30 | 83 | 16·6 | 1870 |
| Large hyaline cells | 6 | 1·2 | 30 | 47 | 9·4 | 990 |
| Mast cells | — | — | — | 1 | 0·2 | 22 |
| Transitional cells | 10 | 2·0 | 60 | 1 | 0·2 | 22 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was abundant. Cells were very numerous and clumped in large masses.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 454 | 90·8 | 37 |
| Coarsely granular polynuclear cells | 18 | 3·6 | 7 |
| Small mononuclear cells | 22 | 4·4 | 1 |
| Large mononuclear cells | 6 | 1·2 | 4 |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 15 | 3·0 | |
| Neutrophilic myelocytes with typical nucleus | 81 | 16·2 | |
| Eosinophilic myelocytes with typical nucleus | 48 | 9·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 8 | 1·6 | |
| Finely granular polynuclear cells | — | — | |
| Coarsely granular polynuclear cells | 1 | 0·2 | |
| Small mononuclear cells | 235 | 47·0 | 62·2 |
| Large mononuclear cells | 76 | 15·2 | |
| Large hyaline cells | 22 | 4·4 | |
| Coarsely granular basophilic cells | 7 | 1·4 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 3 | 0·6 | |
| Transitional cells | 4 | 0·8 | |
| Amphophilic cells | — | — | |
| | 500 | | |

Two normoblasts seen while counting 500 white cells.

## Bacillus aerogenes capsulatus.

EXPERIMENT 6.—*Guinea-pig killed fifteen minutes after an intraperitoneal injection of the bacillus aerogenes capsulatus.*

| **The blood.** | *Physiological blood.* Leucocytes=1300 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes=1600 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 128 | 25·6 | 338 | 143 | 28·6 | 464 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 3 | 1 | 0·2 | 3 |
| Small lymphocytes | 341 | 68·2 | 884 | 337 | 67·4 | 1072 |
| Large lymphocytes | 9 | 1·8 | 26 | 9 | 1·8 | 32 |
| Large hyaline cells | 6 | 1·2 | 13 | 7 | 1·4 | 16 |
| Mast cells | 1 | 0·2 | 3 | 1 | 0·2 | 3 |
| Transitional cells | 14 | 2·8 | 39 | 2 | 0·4 | 6 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was present in large amount.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 2 | 0·4 | — |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 498 | 99·6 | — |
| Large mononuclear cells | — | — | — |
| | 500 | | |

Bacilli were numerous, and no capsulated bacilli seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 77 | 7·7 | |
| Neutrophilic myelocytes with typical nucleus | 215 | 21·5 | |
| Eosinophilic myelocytes with typical nucleus | 57 | 5·7 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 8 | 0·8 | |
| Finely granular polynuclear cells | 22 | 2·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 452 | 45·2 | 57·0 |
| Large mononuclear cells | 118 | 11·8 | |
| Large hyaline cysts | 41 | 4·1 | |
| Coarsely granular basophilic cells | 8 | 0·8 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

One normoblast seen while counting 1000 cells.

EXPERIMENT 7.—*Guinea-pig killed one hour after an intra-peritoneal injection of the bacillus aerogenes capsulatus.*

| **The blood.** | *Physiological blood.* Leucocytes=3500 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes=3500 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 306 | 61·2 | 2135 | 303 | 60·6 | 2135 |
| Coarsely granular polynuclear cells | 44 | 8·8 | 315 | 55 | 11·0 | 385 |
| Small lymphocytes | 81 | 16·2 | 560 | 54 | 10·8 | 385 |
| Large lymphocytes | 22 | 4·4 | 140 | 9 | 1·8 | 70 |
| Large hyaline cells | 43 | 8·6 | 315 | 78 | 15·6 | 560 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 4 | 0·8 | 28 | 1 | 0·2 | 7 |
| | 500 | | | 500 | | |

**Peritoneal fluid.**—No free bacilli seen. Cells very numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 331 | 66·2 | — |
| Coarsely granular polynuclear cells | 1 | 0·2 | — |
| Small mononuclear cells | 166 | 33·2 | — |
| Large mononuclear cells | 2 | 0·4 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 31 | 3·1 | |
| Neutrophilic myelocytes with typical nucleus | 52 | 5·2 | |
| Eosinophilic myelocytes with typical nucleus | 22 | 2·2 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 6 | 0·6 | |
| Finely granular polynuclear cells | 230 | 23·0 | |
| Coarsely granular polynuclear cells | 34 | 3·4 | |
| Small mononuclear cells | 477 | 47·7 | 58·8 |
| Large mononuclear cells | 111 | 11·1 | |
| Large hyaline cells | 20 | 2·0 | |
| Coarsely granular basophilic cells | 17 | 1·7 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Ten normoblasts seen while counting 1000 cells.

EXPERIMENT 8.—*Guinea-pig killed two hours after an intraperitoneal injection of the bacillus aerogenes capsulatus.*

| **The blood.** | *Physiological blood.* Leucocytes = 2300 per c.mm. | | | *Pathological blood.* Leucocytes = 3000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 100 | 20·0 | 460 | 330 | 66·0 | 1980 |
| Coarsely granular polynuclear cells | 59 | 11·8 | 276 | 44 | 8·8 | 270 |
| Small lymphocytes | 160 | 32·0 | 736 | 38 | 7·6 | 240 |
| Large lymphocytes | 70 | 14·0 | 322 | 59 | 11·8 | 360 |
| Large hyaline cells | 109 | 21·8 | 506 | 25 | 5·0 | 150 |
| Mast cells | 2 | 0·4 | 9 | 3 | 0·6 | 18 |
| Transitional cells | — | — | — | 1 | 0·2 | 6 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was present in very large amount. All cells granular. Bacilli very numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 399 | 79·8 | 161 |
| Coarsely granular polynuclear cells | 26 | 5·2 | 6 |
| Small mononuclear cells | 74 | 14·8 | — |
| Large mononuclear cells | 1 | 0·2 | — |
| | 500 | | |

Three mast cells seen. Some of the bacilli which were in the phagocytes were vacuolated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 21 | 2·1 | |
| Neutrophilic myelocytes with typical nucleus | 12 | 1·2 | |
| Eosinophilic myelocytes with typical nucleus | 28 | 2·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 8 | 0·8 | |
| Finely granular polynuclear cells | 54 | 5·4 | |
| Coarsely granular polynuclear cells | 62 | 6·2 | |
| Small mononuclear cells | 684 | 68·4 | 77·9 |
| Large mononuclear cells | 95 | 9·5 | |
| Large hyaline cells | 24 | 2·4 | |
| Coarsely granular basophilic cells | 8 | 0·8 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | 4 | 0·4 | |
| Amphophilic cells | — | — | |
| | 1000 | | |

No organisms seen. No nucleated red cells seen.

EXPERIMENT 9.—*Guinea-pig killed four hours after an intra-peritoneal injection of the bacillus aerogenes capsulatus.*

| **The blood.** | *Physiological blood.* Leucocytes=1300 per c.mm. | | | *Pathological blood.* Leucocytes=4600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 165 | 33·0 | 429 | 400 | 80·0 | 3680 |
| Coarsely granular polynuclear cells | 74 | 14·8 | 195 | 28 | 5·6 | 276 |
| Small lymphocytes. | 184 | 36·8 | 481 | 28 | 5·6 | 276 |
| Large lymphocytes | 62 | 12·4 | 156 | 26 | 5·2 | 230 |
| Large hyaline cells | 13 | 2·6 | 39 | 18 | 3·6 | 184 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 5 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was abundant. No free bacilli seen; leucocytes very numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 410 | 82·0 | — |
| Coarsely granular polynuclear cells | 32 | 6·4 | 3 |
| Small mononuclear cells | 48 | 9·6 | — |
| Large mononuclear cells | 10 | 2·0 | — |
| | 500 | | |

Many of the polynuclear cells were very much degenerated. Only a few free bacilli seen. The bacilli lying in the coarsely granular eosinophilic cells were very much degenerated, and, as usual, only stained feebly with the basic dyes.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 1 | 0·5 | |
| Neutrophilic myelocytes with typical nucleus | 46 | 23·0 | |
| Eosinophilic myelocytes with typical nucleus | 40 | 20·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 10 | 5·0 | |
| Coarsely granular polynuclear cells | 1 | 0·5 | |
| Small mononuclear cells | 73 | 36·5 | 43·5 |
| Large mononuclear cells | 14 | 7·0 | |
| Large hyaline cells | 9 | 4·5 | |
| Coarsely granular basophilic cells | 2 | 1·0 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 2 | 1·0 | |
| Transitional cells | — | — | |
| Amphophilic cells | 2 | 1·0 | |
| | 200 | | |

Cells rather badly stained, therefore count was not strictly accurate.

EXPERIMENT 10.—*Guinea-pig killed six hours after an intra-peritoneal injection of the bacillus aerogenes capsulatus.*

**The blood.**

| | *Physiological blood.* Leucocytes=1600 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes=10,000 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 165 | 33·0 | 528 | 435 | 87·0 | 8700 |
| Coarsely granular polynuclear cells | — | — | — | 1 | 0·2 | 20 |
| Small lymphocytes | 232 | 46·4 | 736 | 33 | 6·6 | 660 |
| Large lymphocytes | 34 | 6·8 | 112 | 11 | 2·2 | 220 |
| Large hyaline cells | 67 | 13·4 | 208 | 20 | 4·0 | 400 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 6 | — | — | — |
| | 500 | | | 500 | | |

Three normoblasts were seen while counting 500 leucocytes. Blood-platelets very numerous. Polynuclear cells were very degenerated, and showed a tendency to form large clumps.

**Peritoneal fluid.** This was abundant and appeared to be milky. Cells very numerous, all granular; one bacillus seen.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 460 | 92·0 | 36[1] |
| Coarsely granular polynuclear cells | 2 | 0·4 | — |
| Small mononuclear cells | 5 | 1·0 | — |
| Large mononuclear cells | 33 | 6·6 | — |
| Large hyaline cells | — | — | — |
| | 500 | | |

Six mast cells were seen while counting 500 cells. The bacilli in the cells were all stained a pale blue and were shrunken and degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 21 | 2·1 | |
| Neutrophilic myelocytes with typical nucleus | 119 | 11·9 | |
| Eosinophilic myelocytes with typical nucleus | 46 | 4·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 9 | 0·9 | |
| Finely granular polynuclear cells | 15 | 1·5 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 560 | 56·0 | 72·2 |
| Large mononuclear cells | 162 | 16·2 | |
| Large hyaline cells | 38 | 3·8 | |
| Coarsely granular basophilic cells | 19 | 1·9 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 11 | 1·1 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Thirteen normoblasts and two megaloblasts were seen while counting 1000 cells.

[1] Most of these cells were degenerated.

EXPERIMENT 11.—*Guinea-pig killed twenty-four hours after an intra-peritoneal injection of the bacillus aerogenes capsulatus.*

| **The blood.** | *Physiological blood.* Leucocytes=4500 per c.mm. | | | *Pathological blood.* Leucocytes=9600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 157 | 31·4 | 1395 | 160 | 32·0 | 3072 |
| Coarsely granular polynuclear cells | 64 | 12·8 | 585 | 21 | 4·2 | 384 |
| Small lymphocytes | 146 | 29·2 | 1305 | 186 | 37·2 | 3552 |
| Large lymphocytes | 57 | 11·4 | 495 | 106 | 21·2 | 2016 |
| Large hyaline cells | 76 | 15·2 | 675 | 24 | 4·8 | 480 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | 3 | 0·6 | 58 |
| | 500 | | | 500 | | |

*No peritoneal fluid* seen. No organisms seen.

**Peritoneal fluid.**

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 451 | 90·2 | — |
| Coarsely granular polynuclear cells | 3 | 0·6 | — |
| Small mononuclear cells | 4 | 0·8 | — |
| Large mononuclear cells | 42 | 8·4 | — |
| | 500 | | |

Cells were degenerated. No bacilli were seen.

*Film preparations from the omentum.*

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 498 | 99·6 | 498 |
| Coarsely granular polynuclear cells | 2 | 0·4 | 2 |
| Small mononuclear cells | — | — | — |
| Large mononuclear cells | — | — | — |
| | 500 | | |

Cells very degenerated. Bacilli stained very pale.

## Bacillus coli (dead).

EXPERIMENT 12.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the above-mentioned bacillus.*

| **The blood.** | *Physiological blood.* Leucocytes=2400 per c.mm. | | | *Pathological blood.* Leucocytes=2300 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 154 | 30·8 | 739·2 | — | — | — |
| Coarsely granular polynuclear cells | 6 | 1·2 | 28·8 | — | — | — |
| Small lymphocytes | 188 | 37·6 | 902·4 | — | — | — |
| Large lymphocytes | 39 | 7·8 | 187·2 | — | — | — |
| Large hyaline cells | 110 | 22·0 | 528·0 | — | — | — |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 3 | 0·6 | 14·4 | — | — | — |
| | 500 | | | | | |

**Peritoneal fluid.** This was abundant.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 1 | 0·2 | — |
| Coarsely granular polynuclear cells | 1 | 0·2 | — |
| Small mononuclear cells | 463 | 92·6 | 10 |
| Large mononuclear cells | 35 | 7·0 | 3 |
| | 500 | | |

All the cells in good condition; very many free bacilli seen.

**Bone-marrow** (*femur*).

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 25 | 5·0 | |
| Neutrophilic myelocytes with typical nucleus | 39 | 7·8 | |
| Eosinophilic myelocytes with typical nucleus | 7 | 1·4 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 6 | 1·2 | |
| Finely granular polynuclear cells | 15 | 3·0 | |
| Coarsely granular polynuclear cells | 3 | 0·6 | |
| Small mononuclear cells | 258 | 51·6 | 73·8 |
| Large mononuclear cells | 111 | 22·2 | |
| Large hyaline cells | 19 | 3·8 | |
| Coarsely granular basophilic cells | 5 | 1·0 | |
| Finely granular basophilic cells | 6 | 1·2 | |
| Giant cells | 6 | 1·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

Three normoblasts were seen while counting 500 cells.

EXPERIMENT 13.—*Guinea-pig killed one hour after an intraperitoneal injection of the above-mentioned bacillus.*

| **The blood.** | *Physiological blood.* Leucocytes = 5500 per c.mm. | | | *Pathological blood.* Leucocytes = 2400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 126 | 25·2 | 1386 | 287 | 57·4 | 1368 |
| Coarsely granular polynuclear cells | 3 | 0·6 | 33 | 4 | 0·8 | 19 |
| Small lymphocytes | 219 | 43·8 | 2420 | 138 | 27·6 | 672 |
| Large lymphocytes | 80 | 16·0 | 880 | 23 | 4·6 | 120 |
| Large hyaline cells | 70 | 14·0 | 610 | 48 | 9·6 | 240 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 22 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was abundant. Very numerous free bacilli seen. Cells were scarce.

| | Total No. | No. phagocytic. |
|---|---|---|
| Finely granular polynuclear cells | 271 | 24 |
| Coarsely granular polynuclear cells | 61 | 8 |
| Small mononuclear cells | 97 | — |
| Large mononuclear cells | 10 | — |
| | 439 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 4 | 0·4 | |
| Neutrophilic myelocytes with typical nucleus | 1 | 0·1 | |
| Eosinophilic myelocytes with typical nucleus | — | — | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 5 | 0·5 | |
| Finely granular polynuclear cells | 286 | 28·6 | |
| Coarsely granular polynuclear cells | 75 | 7·5 | |
| Small mononuclear cells | 433 | 43·3 | 59·3 |
| Large mononuclear cells | 160 | 16·0 | |
| Large hyaline cells | 22 | 2·2 | |
| Coarsely granular basophilic cells | 14 | 1·4 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

EXPERIMENT 14.—*Guinea-pig killed two hours after an intraperitoneal injection of the above-mentioned bacillus.*

| **The blood.** | *Physiological blood.* Leucocytes=4600 per c.mm. | | | *Pathological blood.* Leucocytes=2100 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 203 | 40·6 | 1886 | 92 | 30·66 | 651 |
| Coarsely granular polynuclear cells | 7 | 1·4 | 46 | 26 | 8·66 | 189 |
| Small lymphocytes | 162 | 32·4 | 1472 | 90 | 30·0 | 630 |
| Large lymphocytes | 33 | 6·6 | 302 | 30 | 10·0 | 210 |
| Large hyaline cells | 95 | 19·0 | 874 | 60 | 20·0 | 420 |
| Mast cells | — | — | — | 1 | 0·33 | 6 |
| Transitional cells | — | — | — | 1 | 0·33 | 6 |
| | 500 | | | 300 | | |

**Peritoneal fluid.** This was abundant. No agglutination of cells was seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 105 | 26·25 | 6 |
| Coarsely granular polynuclear cells | 248 | 62·0 | 93 |
| Small mononuclear cells | 46 | 11·5 | 1 |
| Large mononuclear cells | 1 | 0·25 | — |
| Large hyaline cells | — | — | — |
| | 400 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 16 | 1·6 | |
| Neutrophilic myelocytes with typical nucleus | 137 | 13·7 | |
| Eosinophilic myelocytes with typical nucleus | 21 | 2·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 19 | 1·9 | |
| Finely granular polynuclear cells | 8 | 0·8 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 583 | 58·3 | 75·5 |
| Large mononuclear cells | 172 | 17·2 | |
| Large hyaline cells | 37 | 3·7 | |
| Coarsely granular basophilic cells | 1 | 0·1 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 5 | 0·5 | |
| Transitional cells | 1 | 0·1 | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Three megaloblasts and nine normoblasts were seen while counting 1000 cells.

EXPERIMENT 15.—*Guinea-pig killed four hours after an intra-peritoneal injection of the above-mentioned bacillus.*

| **The blood.** | *Physiological blood.* Leucocytes = 7200 per c.mm. | | | *Pathological blood.* Leucocytes = 5400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 324 | 64·8 | 4680 | 320 | 64·0 | 3456 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 14 | 2 | 0·4 | 21 |
| Small lymphocytes | 88 | 17·6 | 1296 | 97 | 19·4 | 1026 |
| Large lymphocytes | 17 | 3·4 | 216 | 21 | 4·2 | 216 |
| Large hyaline cells | 66 | 13·2 | 936 | 60 | 12·0 | 648 |
| Mast cells | 1 | 0·2 | 14 | — | — | — |
| Transitional cells | 3 | 0·6 | 43 | — | — | — |
| | 500 | | | | | |

**Blood-platelets** were very numerous.

**Peritoneal fluid.** This was abundant. Agglutination of cells was well marked.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 435 | 87·0 |
| Coarsely granular polynuclear cells | 5 | 1·0 |
| Small mononuclear cells | 23 | 4·6 |
| Large mononuclear cells | 37 | 7·4 |
| | 500 | |

No micro-organisms were seen. Cells were in excellent condition.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 129 | 12·9 | |
| Neutrophilic myelocytes with typical nucleus | 212 | 21·2 | |
| Eosinophilic myelocytes with typical nucleus | 21 | 2·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 5 | 0·5 | |
| Finely granular polynuclear cells | 32 | 3·2 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 421 | 42·1 | 55·2 |
| Large mononuclear cells | 131 | 13·1 | |
| Large hyaline cells | 32 | 3·2 | |
| Coarsely granular basophilic cells | 5 | 0·5 | |
| Finely granular basophilic cells | 6 | 0·6 | |
| Giant cells | 6 | 0·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Four normoblasts and three megaloblasts were seen while counting 1000 cells.

EXPERIMENT 16.—*Guinea-pig killed six hours after an intra-peritoneal injection of the above-mentioned bacillus.*

| **The blood.** | *Physiological blood.* Leucocytes = 6800 per c.mm. | | | *Pathological blood.* Leucocytes = 4600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 187 | 37·4 | 2516 | 236 | 47·2 | 2162 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 13 | 14 | 2·8 | 138 |
| Small lymphocytes | 162 | 32·4 | 2176 | 227 | 45·4 | 2070 |
| Large lymphocytes | 47 | 9·4 | 612 | 12 | 2·4 | 92 |
| Large hyaline cells | 102 | 20·4 | 1360 | 5 | 1·0 | 46 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 1 | 0·2 | 13 | 6 | 1·2 | 46 |
| | 500 | | | 500 | | |

**Blood-platelets** were very numerous.

**Peritoneal fluid.** This was very turbid. Cells were very numerous. Agglutination of cells was well shown.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 361 | 72·2 | 16 |
| Coarsely granular polynuclear cells | 62 | 12·4 | 7 |
| Small mononuclear cells | 67 | 13·4 | — |
| Large mononuclear cells | 10 | 2·0 | — |
| | 500 | | |

Numerous free bacilli were seen, and many of these were degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 22 | 2·2 | |
| Neutrophilic myelocytes with typical nucleus | 99 | 9·9 | |
| Eosinophilic myelocytes with typical nucleus | 23 | 2·3 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 18 | 1·8 | |
| Finely granular polynuclear cells | 4 | 0·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 607 | 60·7 | 76·7 |
| Large mononuclear cells | 160 | 16·0 | |
| Large hyaline cells | 49 | 4·9 | |
| Coarsely granular basophilic cells | 6 | 0·6 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 11 | 1·1 | |
| Transitional cells | — | — | |
| Amphophilic cells | 1 | 0·1 | |
| | 1000 | | |

Three normoblasts and six megaloblasts were seen while counting 1000 cells.

EXPERIMENT 17.—*Guinea-pig killed twenty-four hours after an intra-peritoneal injection of the above-mentioned bacillus.*

| **The blood.** | *Physiological blood.* Leucocytes=1800 per c.mm. | | | *Pathological blood.* Leucocytes=4200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 194 | 38·8 | 702 | 348 | 69·6 | 2940 |
| Coarsely granular polynuclear cells | 6 | 1·2 | 18 | 1 | 0·2 | 8 |
| Small lymphocytes | 187 | 37·4 | 666 | 54 | 10·8 | 462 |
| Large lymphocytes | 48 | 9·6 | 180 | 17 | 3·4 | 126 |
| Large hyaline cells | 65 | 13·0 | 234 | 73 | 14·6 | 630 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | 7 | 1·4 | 42 |
| | 500 | | | 500 | | |

**No peritoneal fluid** was seen. Large numbers of cells were present.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 488 | 97·6 | — |
| Coarsely granular polynuclear cells | 2 | 0·4 | — |
| Small mononuclear cells | 1 | 0·2 | — |
| Large mononuclear cells | 9 | 1·8 | — |
| | 500 | | |

No free bacilli were seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 14 | 1·4 | |
| Neutrophilic myelocytes with typical nucleus | 2 | 0·2 | |
| Eosinophilic myelocytes with typical nucleus | 4 | 0·4 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 0·3 | |
| Finely granular polynuclear cells | 133 | 13·3 | |
| Coarsely granular polynuclear cells | 46 | 4·6 | |
| Small mononuclear cells | 683 | 68·3 | 76·4 |
| Large mononuclear cells | 81 | 8·1 | |
| Large hyaline cells | 32 | 3·2 | |
| Coarsely granular basophilic cells | 2 | 0·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Fifteen normoblasts and one megaloblast were seen while counting 1000 cells.

EXPERIMENT 18.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the bacillus coli.*

| **The blood.** | *Physiological blood.* Leucocytes = 4600 per c.mm. | | | *Pathological blood.* Leucocytes = 6000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 206 | 41·2 | 1886 | 169 | 33·8 | 2040 |
| Coarsely granular polynuclear cells | 11 | 2·2 | 92 | 15 | 3·0 | 180 |
| Small lymphocytes | 272 | 54·4 | 2484 | 10 | 2·0 | 120 |
| Large lymphocytes | 1 | 0·2 | 9·2 | 180 | 36·0 | 2160 |
| Large hyaline cells | 5 | 1·0 | 46 | 124 | 24·8 | 1500 |
| Mast cells | — | — | — | 2 | 0·4 | 24 |
| Transitional cells | 5 | 1·0 | 46 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid** was scanty. Very few cells were seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 1 | 0·2 | — |
| Coarsely granular polynuclear cells | 379 | 75·8 | 16 |
| Small mononuclear cells | 105 | 21·0 | 2 |
| Large mononuclear cells | 15 | 3·0 | — |
| | 500 | | |

All the cells were in good condition. No free bacilli were seen, and very few of the cells were phagocytic.

**Bone-marrow (femur).**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 50 | 5·0 | |
| Neutrophilic myelocytes with typical nucleus | 247 | 24·7 | |
| Eosinophilic myelocytes with typical nucleus | 40 | 4·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 21 | 2·1 | |
| Finely granular polynuclear cells | 56 | 5·6 | |
| Coarsely granular polynuclear cells | 3 | 0·3 | |
| Small mononuclear cells | 305 | 30·5 | 51·3 |
| Large mononuclear cells | 208 | 20·8 | |
| Large hyaline cells | 42 | 4·2 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 10 | 1·0 | |
| Transitional cells | 11 | 1·1 | |
| Amphophilic cells | 7 | 0·7 | |
| | 1000 | | |

No nucleated red cells were seen.

EXPERIMENT 19.—*Guinea-pig killed one hour after an intraperitoneal injection of the bacillus coli.*

| **The blood.** | *Physiological blood.* Leucocytes=2000 per c.mm. | | | *Pathological blood.* Leucocytes=2400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 214 | 35·6 | 720 | 166 | 41·5 | 984 |
| Coarsely granular polynuclear cells | 2 | 0·3 | 6 | 2 | 0·5 | 12 |
| Small lymphocytes | 90 | 15·0 | 300 | 29 | 7·25 | 168 |
| Large lymphocytes | 180 | 30·0 | 600 | 144 | 36·0 | 864 |
| Large hyaline cells | 104 | 17·3 | 340 | 59 | 14·75 | 360 |
| Mast cells | 6 | 1·0 | 20 | — | — | — |
| Transitional cells | 4 | 0 6 | 12 | — | — | — |
| | 600 | | | 400 | | |

**Peritoneal fluid.** This was abundant. The cells were numerous and large numbers of bacilli were present.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 288 | 57·6 | 284 |
| Coarsely granular polynuclear cells | 4 | 0·8 | 3 |
| Small mononuclear cells | 194 | 38·8 | 29 |
| Large mononuclear cells | 12 | 2·4 | 4 |
| Transitional cells | 2 | 0·4 | 2 |
| | 500 | | |

While counting 500 cells eight groups of agglutinated finely granular polynuclear cells were seen. Free bacilli were very numerous and "Pfeiffer's phenomenon" was well marked. The finely granular polynuclear cells were much degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 41 | 4·1 | |
| Neutrophilic myelocytes with typical nucleus | 145 | 14·5 | |
| Eosinophilic myelocytes with typical nucleus | 11 | 1·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 7 | 0·7 | |
| Finely granular polynuclear cells | 127 | 12 7 | |
| Coarsely granular polynuclear cells | 5 | 0·5 | |
| Small mononuclear cells | 280 | 28·0 | 53·0 |
| Large mononuclear cells | 250 | 25·0 | |
| Large hyaline cells | 91 | 9·1 | |
| Coarsely granular basophilic cells | 19 | 1·9 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 19 | 1·9 | |
| Transitional cells | 3 | 0·3 | |
| Amphophilic cells | 2 | 0·2 | |
| | 1000 | | |

Ten normoblasts, thirteen megaloblasts, and three gigantoblasts were seen while counting 1000 cells. No bacilli were seen. Polychromatophilic degeneration was well marked.

EXPERIMENT 20.—*Guinea-pig killed two hours after an intraperitoneal injection of the bacillus coli.*

**The blood.**

| | *Physiological blood.* Leucocytes = 3000 per c.mm. | | | *Pathological blood.* Leucocytes = 4800 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 234 | 46·8 | 1410 | 241 | 48·2 | 2304 |
| Coarsely granular polynuclear cells | 3 | 0·6 | 18 | 19 | 3·8 | 192 |
| Small lymphocytes | 240 | 48·0 | 1440 | 79 | 15·8 | 768 |
| Large lymphocytes | 8 | 1·6 | 48 | 76 | 15·2 | 720 |
| Large hyaline cells | 8 | 1·6 | 48 | 82 | 16·4 | 768 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 7 | 1·4 | 42 | 3 | 0·6 | 288 |
| | 500 | | | 500 | | |

**Blood-platelets** were numerous and polychromatophilic degeneration was well marked.

**Peritoneal fluid.** This was very abundant. The bacilli were actively motile and in small clumps. The cells were also in small clumps, but scarce.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 132 | 66 | 132 |
| Coarsely granular polynuclear cells | 26 | 13 | 26 |
| Small mononuclear cells | 40 | 20 | 3 |
| Large mononuclear cells | 2 | 1 | 1 |
| | 200 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 7 | 0·7 | |
| Neutrophilic myelocytes with typical nucleus | 29 | 2·9 | |
| Eosinophilic myelocytes with typical nucleus | 9 | 0·9 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 2 | 0·2 | |
| Finely granular polynuclear cells | 96 | 9·6 | |
| Coarsely granular polynuclear cells | 38 | 3·8 | |
| Small mononuclear cells | 705 | 70·5 | 79·1 |
| Large mononuclear cells | 86 | 8·6 | |
| Large hyaline cells | 19 | 1·9 | |
| Coarsely granular basophilic cells | 9 | 0·9 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Seven normoblasts and one vacuolated large hyaline cell were seen while counting 1000 white cells. No bacilli were seen.

EXPERIMENT 20 A.—*Guinea-pig killed two hours after an intra-peritoneal injection of the bacillus coli.*

**The blood.**

| | *Physiological blood.* Leucocytes=3700 per c.mm. | | | *Pathological blood.* Leucocytes=4100 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 30 | 6·0 | 222 | 325 | 54·166 | 2214 |
| Coarsely granular polynuclear cells | 26 | 5·2 | 185 | 29 | 4·833 | 369 |
| Small lymphocytes | 388 | 61·6 | 2294 | 211 | 35·166 | 1435 |
| Large lymphocytes | 117 | 23·4 | 851 | 10 | 1·666 | 82 |
| Large hyaline cells | 11 | 2·2 | 74 | 3 | 0·5 | 20·5 |
| Mast cells | 2 | 0·4 | 14·8 | 2 | 0·333 | 13·653 |
| Transitional cells | 6 | 1·2 | 37 | 20 | 3·333 | 123 |
| | 500 | | | 600 | | |

**Peritoneal fluid.** This was abundant. Cells were numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 49 | 9·8 | 19 |
| Coarsely granular polynuclear cells | 411 | 82·2 | 208 |
| Small mononuclear cells | 37 | 7·4 | 2 |
| Large mononuclear cells | 2 | 0·4 | 2 |
| Transitional cells | 1 | 0·2 | 1 |
| | 500 | | |

EXPERIMENT 21.—*Guinea-pig killed four hours after an intra-peritoneal injection of the bacillus coli.*

**The blood.**

| | *Physiological blood.* Leucocytes = 5900 per c.mm. | | | *Pathological blood.* Leucocytes = 6000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 138 | 34·5 | 2065 | 283 | 56·6 | 3420 |
| Coarsely granular polynuclear cells | 32 | 8·0 | 472 | 5 | 1·0 | 60 |
| Small lymphocytes | 3 | 0·75 | 44·25 | 197 | 39·4 | 2340 |
| Large lymphocytes | 170 | 42·5 | 2478 | 2 | 0·4 | 24 |
| Large hyaline cells | 44 | 11·0 | 649 | 9 | 1·8 | 108 |
| Mast cells | 13 | 3·25 | 177 | — | — | — |
| Transitional cells | — | — | — | 4 | 0·8 | 48 |
| | 400 | | | 500 | | |

**Peritoneal fluid.** This was abundant. Dense masses of cells were seen lying in large clumps. Enormous numbers of non-motile bacilli present.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 456 | 91·2 | 357 |
| Coarsely granular polynuclear cells | 28 | 5·6 | 15 |
| Small mononuclear cells | 11 | 2·2 | 1 |
| Large mononuclear cells | — | — | — |
| Large hyaline cells | 5 | 1·0 | 5 |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 3 | 0·6 | |
| Neutrophilic myelocytes with typical nucleus | 156 | 31·2 | |
| Eosinophilic myelocytes with typical nucleus | 60 | 12·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·2 | |
| Finely granular polynuclear cells | 12 | 2·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 141 | 28·2 | 45 |
| Large mononuclear cells | 84 | 16·8 | |
| Large hyaline cells | 24 | 4·8 | |
| Coarsely granular basophilic cells | 9 | 1·8 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 2 | 0·4 | |
| Transitional cells | — | — | |
| Amphophilic cells | 8 | 1·6 | |
| | 500 | | |

Seven normoblasts were seen while counting 500 white cells.

EXPERIMENT 21A.—*Guinea-pig killed four hours after an intraperitoneal injection of the bacillus coli.*

| **The blood.** | *Physiological blood.* Leucocytes=3600 per c.mm. | | | *Pathological blood.* Leucocytes=3800 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 53 | 10·6 | 396 | 294 | 58·8 | 2242 |
| Coarsely granular polynuclear cells | 47 | 9·4 | 324 | 84 | 16·8 | 646 |
| Small lymphocytes | 298 | 59·6 | 2160 | 74 | 14·8 | 570 |
| Large lymphocytes | 89 | 17·8 | 648 | 33 | 6·6 | 266 |
| Large hyaline cells | 7 | 1·4 | 36 | 15 | 3·0 | 114 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 4 | 0·8 | 28·8 | — | — | — |
| Vacuolated cells | 2 | 0·4 | 14·4 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was abundant and turgid. Cells were very numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 131 | 26·2 | 131 |
| Coarsely granular polynuclear cells | 355 | 71·0 | 246 |
| Small mononuclear cells | 11 | 2·2 | 7 |
| Large mononuclear cells | 3 | 0·6 | 2 |
| | 500 | | |

Cells were very degenerated. Bacilli were often ill-defined and beaded, and also showed irregular staining, polar staining, and vacuolation in those inside the cells.

EXPERIMENT 22.—*Guinea-pig killed eight hours after an intraperitoneal injection of the bacillus coli.*

| **The blood.** | *Physiological blood.* Leucocytes=5400 per c.mm. | | | *Pathological blood.* Leucocytes=2000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 183 | 36·6 | 1998 | 130 | 26·0 | 520 |
| Coarsely granular polynuclear cells | 2 | 0·4 | 21·6 | 10 | 2·0 | 40 |
| Small lymphocytes | 203 | 40·6 | 2160 | 275 | 55·0 | 1100 |
| Large lymphocytes | 71 | 14·2 | 756 | 63 | 12·6 | 260 |
| Large hyaline cells | 40 | 8·0 | 432 | 12 | 2·4 | 40 |
| Mast cells | — | — | — | 1 | 0·2 | 4 |
| Transitional cells | 1 | 0·2 | 10·8 | 9 | 1·8 | 40 |
| | 500 | | | 500 | | |

Numerous bacilli were seen in the blood, but no cells were shown to be phagocytic.

**Peritoneal fluid.** This was scanty.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 194 | 57·6 | 194 |
| Coarsely granular polynuclear cells | 20 | 8 | 16 |
| Small mononuclear cells | 22 | 8·8 | 10 |
| Large mononuclear cells | 14 | 5·6 | 12 |
| Degenerated cells | 12 | 4·8 | 12 |
| | 262 | | |

Very few cells were obtained from the films.

EXPERIMENT 23.—*Guinea-pig killed seventeen hours after an intraperitoneal injection of the bacillus coli.*

| **The blood.** | *Physiological blood.* Leucocytes=2700 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes=3900 per c.mm. |
|---|---|---|---|---|
| Finely granular polynuclear cells | 74 | 14·8 | 405 | |
| Coarsely granular polynuclear cells | 39 | 7·8 | 216 | The cells were so degenerated that it was |
| Small lymphocytes | 339 | 67·8 | 1836 | impossible to form any |
| Large lymphocytes | 34 | 6·8 | 189 | accurate idea as to |
| Large hyaline cells | 10 | 2·0 | 54 | their nature. |
| Mast cells | — | — | — | |
| Transitional cells | — | — | — | |
| Vacuolated cells | 4 | 0·8 | 21·6 | |
| | 500 | | | |

**Peritoneal fluid.** This was abundant and very turbid. The cells were very numerous and the phagocytic reaction was well marked. Many bacilli appeared to be degenerated.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 460 | 92 | 459 |
| Coarsely granular polynuclear cells | 21 | 4·2 | 7 |
| Small mononuclear cells | 9 | 1·8 | 4 |
| Large mononuclear cells | 10 | 2·0 | 10 |
| | 500 | | |

Many of the bacilli were definitely capsulated, while beading and pale staining were well marked.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 30 | 6·0 | |
| Neutrophilic myelocytes with typical nucleus | 18 | 3·6 | |
| Eosinophilic myelocytes with typical nucleus | 7 | 1·4 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 7 | 1·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 350 | 70·0 | 83·6 |
| Large mononuclear cells | 68 | 13·6 | |
| Large hyaline cells | 8 | 1·6 | |
| Coarsely granular basophilic cells | 1 | 0·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 11 | 2·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells seen.

EXPERIMENT 24.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the bacillus pyocyaneus.*

| **The blood.** | *Physiological blood.* Leucocytes=1400 per c.mm. | | | *Pathological blood.* Leucocytes=1400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 106 | 21·2 | 294 | 111 | 22·2 | 308 |
| Coarsely granular polynuclear cells | 10 | 2·0 | 28 | 35 | 7·0 | 98 |
| Small lymphocytes | 252 | 50·4 | 700 | 267 | 53·4 | 742 |
| Large lymphocytes | 118 | 23·6 | 336 | 60 | 12·0 | 168 |
| Large hyaline cells | 14 | 2·8 | 42 | 23 | 4·6 | 70 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | 4 | 0·8 | 12 |
| | 500 | | | 500 | | |

**Peritoneal fluid.**—Free motile bacilli were seen, and one or two cells were observed to be phagocytic.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | — | — | — |
| Coarsely granular polynuclear cells | 7 | 1·4 | 6 |
| Small mononuclear cells | 487 | 97·4 | 3 |
| Large mononuclear cells | 3 | 0·6 | 1 |
| Transitional cells | 3 | 0·6 | — |
| | 500 | | |

EXPERIMENT 25.—*Guinea-pig killed one hour after an intra-peritoneal injection of the bacillus pyocyaneus.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes=2300 per c.mm. | | | Leucocytes=3300 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 263 | 52·6 | 1219 | 295 | 59 | 1947 |
| Coarsely granular polynuclear cells | 70 | 14·0 | 322 | 67 | 13·4 | 429 |
| Small lymphocytes | 148 | 29·6 | 690 | 126 | 25·2 | 825 |
| Large lymphocytes | 7 | 1·4 | 23 | 1 | 0·2 | 6·6 |
| Large hyaline cells | 1 | 0·2 | 4·6 | 1 | 0·2 | 6·6 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 11 | 2·2 | 46 | 10 | 2·0 | 66 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was fairly abundant. Many more cells were phagocytic than in Experiment 24.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 143 | 28·6 | 111 |
| Coarsely granular polynuclear cells | 187 | 37·4 | 148 |
| Small mononuclear cells | 143 | 28·6 | 11 |
| Large mononuclear cells | 12 | 2·4 | 3 |
| Mast cells | 3 | 0·6 | 2 |
| Degenerated cells | 12 | 2·4 | — |
| | 500 | | |

EXPERIMENT 26.—*Guinea-pig killed two hours after an intra-peritoneal injection of the bacillus pyocyaneus.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes=4300 per c.mm. | | | Leucocytes=4600 per c.mm. | | |
| | Total No. | Per c.mm. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 261 | 52·2 | 2236 | 421 | 84·2 | 3864 |
| Coarsely granular polynuclear cells | 41 | 8·2 | 344 | 18 | 3·6 | 184 |
| Small lymphocytes | 153 | 30·6 | 1333 | 51 | 10·2 | 460 |
| Large lymphocytes | 14 | 2·8 | 129 | 2 | 0·4 | 18·4 |
| Large hyaline cells | 4 | 0·8 | 34 | 3 | 0·6 | 27·6 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 27 | 5·4 | 215 | 5 | 1·0 | 46 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was very abundant. The cells showed very marked phagocytosis.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 252 | 50·4 | 252 |
| Coarsely granular polynuclear cells | 206 | 41·2 | 199 |
| Small mononuclear cells | 20 | 4·0 | 1 |
| Large mononuclear cells | 14 | 2·8 | 7 |
| Degenerated cells | 8 | 1·6 | 8 |
| | 500 | | |

Six mast cells were seen, and three of them were noted to be phagocytic, while counting 500 leucocytes. Some of the eosinophile cells were large and degenerated, while others were small and shrunken.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 8 | 4·0 | |
| Neutrophilic myelocytes with typical nucleus | 40 | 20·0 | |
| Eosinophilic myelocytes with typical nucleus | 33 | 16·5 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·5 | |
| Finely granular polynuclear cells | 5 | 2·5 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 71 | 35·5 | 47·5 |
| Large mononuclear cells | 24 | 12·0 | |
| Large hyaline cells | 14 | 7·0 | |
| Coarsely granular basophilic cells | 2 | 1·0 | |
| Finely granular polynuclear cells | 2 | 1·0 | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 200 | | |

One normoblast seen while counting 200 cells.

EXPERIMENT 27.—*Guinea-pig killed six hours after an intra-peritoneal injection of the bacillus pyocyaneus.*

| **The blood.** | *Physiological blood.* Leucocytes=9400 per c.mm. | | | *Pathological blood.* Leucocytes=9800 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 186 | 37·2 | 3478 | 310 | 62·0 | 6076 |
| Coarsely granular polynuclear cells | 42 | 8·4 | 752 | 17 | 3·4 | 294 |
| Small lymphocytes | 155 | 31·0 | 2914 | 36 | 7·2 | 686 |
| Large lymphocytes | 91 | 18·2 | 1692 | 88 | 17·6 | 1764 |
| Large hyaline cells | 23 | 4·6 | 470 | 47 | 9·4 | 882 |
| Mast cells | 3 | 0·6 | 56 | 2 | 0·4 | 39 |
| Transitional cells | — | — | — | — | — | — |
| | 500 | | | 500 | | |

While counting 500 cells, six finely granular polynuclear cells were seen containing bacilli; these cells were very much degenerated.

**Peritoneal fluid.** This was very slightly turbid.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 444 | 88·8 | 370 |
| Coarsely granular polynuclear cells | 22 | 4·4 | 19 |
| Small mononuclear cells | 29 | 5·8 | — |
| Large mononuclear cells | 1 | 0·2 | — |
| Transitional cells | 4 | 0·8 | — |
| | 500 | | |

EXPERIMENT 28.—*Guinea-pig killed eight hours after an intra-peritoneal injection of the bacillus pyocyaneus.*

| **The blood.** | *Physiological blood.* Leucocytes=2400 per c.mm. | | | *Pathological blood.* Leucocytes=3600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 267 | 53·4 | 1272 | 400 | 80·0 | 2880 |
| Coarsely granular polynuclear cells | 13 | 2·6 | 72 | 8 | 1·6 | 72 |
| Small lymphocytes | 190 | 38·0 | 912 | 46 | 9·2 | 324 |
| Large lymphocytes | 12 | 2·4 | 48 | 18 | 3·6 | 144 |
| Large hyaline cells | 6 | 1·2 | 24 | 28 | 5·6 | 216 |
| Mast cells | 1 | 0·2 | 5 | — | — | — |
| Transitional cells | 11 | 2·2 | 48 | — | — | — |
| | 500 | | | 500 | | |

The finely granular and the coarsely granular polynuclear cells were very much degenerated; the nuclei were irregular and the granules extra-cellular. No bacilli were seen.

**Peritoneal fluid.** This was abundant and turbid. Cells numerous and phagocytosis well marked.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 404 | 80·8 | 404 |
| Coarsely granular polynuclear cells | 38 | 7·6 | 36 |
| Small mononuclear cells | 41 | 8·2 | 1 |
| Large mononuclear cells | 5 | 1·0 | 3 |
| Degenerated cells | 12 | 2·4 | 12 |
| | 500 | | |

EXPERIMENT 29.—*Guinea-pig killed twenty-four hours after an intra-peritoneal injection of the bacillus pyocyaneus.*

| **The blood.** | *Physiological blood.* Leucocytes = 3500 per c.mm. | | | *Pathological blood.* Leucocytes = 6500 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 264 | 52·8 | 2065 | 352 | 70·4 | 4550 |
| Coarsely granular polynuclear cells | 9 | 1·8 | 70 | — | — | — |
| Small lymphocytes | 96 | 19·2 | 665 | 46 | 9·2 | 595 |
| Large lymphocytes | 54 | 10·8 | 385 | 62 | 12·4 | 780 |
| Large hyaline cells | 75 | 15·0 | 525 | 39 | 7·8 | 520 |
| Mast cells | 1 | 0·2 | 7 | — | — | — |
| Transitional cells | 1 | 0·2 | 7 | 1 | 0·2 | 13 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was abundant and turbid. There were signs of purulent peritonitis; the cells were very numerous, but there was no true agglutination to be seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 387 | 77·4 | — |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 34 | 6·8 | — |
| Large mononuclear cells | 79 | 15·8 | — |
| | 500 | | |

The cells were in fairly good condition. No micro-organisms were seen. Two of the large mononuclear cells contained finely granular polynuclear cells.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 3 | 0·6 | |
| Neutrophilic myelocytes with typical nucleus | 68 | 13·6 | |
| Eosinophilic myelocytes with typical nucleus | 29 | 5·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | — | — | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 269 | 53·8 | 75·4 |
| Large mononuclear cells | 108 | 21·6 | |
| Large hyaline cells | 17 | 3·4 | |
| Coarsely granular basophilic cells | 5 | 1·0 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | 1 | 0·2 | |
| | 500 | | |

While counting 500 cells, four normoblasts were seen. No bacilli were noted.

EXPERIMENT 30.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the toxins of the bacillus pyocyaneus.*

| **The blood.** | *Physiological blood.* Leucocytes = 0·800 per c.mm. | | | *Pathological blood.* Leucocytes = 1·100 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 167 | 33·4 | 264 | 135 | 27·0 | 297 |
| Coarsely granular polynuclear cells | — | — | — | 1 | 0·2 | 2 |
| Small lymphocytes | 140 | 28 | 224 | 112 | 22·4 | 242 |
| Large lymphocytes | 89 | 17·8 | 144 | 183 | 36·6 | 407 |
| Large hyaline cells | 102 | 20·4 | 160 | 67 | 13·4 | 143 |
| Mast cells | — | — | — | 1 | 0·2 | 2 |
| Transitional cells | 2 | 0·4 | 3 | 1 | 0·2 | 2 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was very abundant and clear; very few cells seen.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | — | — |
| Coarsely granular polynuclear cells | 2 | 1·027 |
| Small mononuclear cells | 191 | 97·4 |
| Large mononuclear cells | 2 | 1·827 |
| | 195 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 34 | 6·8 | |
| Neutrophilic myelocytes with typical nucleus | 106 | 21·2 | |
| Eosinophilic myelocytes with typical nucleus | 22 | 4·4 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 0·6 | |
| Finely granular polynuclear cells | 33 | 6·6 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 207 | 41·4 | 56·6 |
| Large mononuclear cells | 76 | 15·2 | |
| Large hyaline cells | 17 | 3·4 | |
| Coarsely granular basophilic cells | 1 | 0·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 1 | 0·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells seen.

EXPERIMENT 31.—*Guinea-pig killed one hour after an intra-peritoneal injection of the above-mentioned toxins.*

**The blood.**

| | *Physiological blood.* Leucocytes=2·400 per c.mm. | | | *Pathological blood.* Leucocytes=2·900 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 134 | 26·8 | 648 | 230 | 46·0 | 1334 |
| Coarsely granular polynuclear cells | 2 | 0·4 | 9 | 3 | 0·6 | 17 |
| Small lymphocytes | 127 | 25·4 | 600 | 41 | 8·2 | 232 |
| Large lymphocytes | 89 | 17·8 | 432 | 170 | 34·0 | 986 |
| Large hyaline cells | 145 | 29·0 | 696 | 52 | 10·4 | 319 |
| Mast cells | — | — | — | 3 | 0·6 | 17 |
| Transitional cells | 3 | 0·6 | 14 | 1 | 0·2 | 5 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was present in fair quantity and quite clear. Only a few cells were seen.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 251 | 50·2 |
| Coarsely granular polynuclear cells | 77 | 15·4 |
| Small mononuclear cells | 171 | 34·2 |
| Large mononuclear cells | 1 | 0·2 |
| Large hyaline cells | — | — |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 34 | 6·8 | |
| Neutrophilic myelocytes with typical nucleus | 128 | 25·6 | |
| Eosinophilic myelocytes with typical nucleus | 7 | 1·4 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 0·6 | |
| Finely granular polynuclear cells | 47 | 9·4 | |
| Coarsely granular polynuclear cells | 1 | 0·2 | |
| Small mononuclear cells | 166 | 33·2 | 51·2 |
| Large mononuclear cells | 90 | 18·0 | |
| Large hyaline cells | 22 | 4·4 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 2 | 0·4 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells were seen.

EXPERIMENT 32.—*Guinea-pig killed two hours after an intra-peritoneal injection of the above-mentioned toxins.*

| **The blood.** | *Physiological blood.* Leucocytes = 1800 per c.mm. | | *Pathological blood.* Leucocytes = 3100 per c.mm. | | |
|---|---|---|---|---|---|
| | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 34·0 | 612 | 311 | 62·2 | 1922 |
| Coarsely granular polynuclear cells | — | — | — | — | — |
| Small lymphocytes | 35·0 | 630 | 31 | 6·2 | 186 |
| Large lymphocytes | 18·0 | 334 | 83 | 16·6 | 527 |
| Large hyaline cells | 13·0 | 234 | 74 | 14·8 | 465 |
| Mast cells | — | — | 1 | 0·2 | 6 |
| Transitional cells | — | — | — | — | — |
| | | | 500 | | |

One normoblast seen. *Many of the large hyaline cells contain red blood corpuscles.*

**Peritoneal fluid.** This was present in large quantity. Only a few cells seen which lie in clumps.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 474 | 94·8 |
| Coarsely granular polynuclear cells | 2 | 0·4 |
| Small mononuclear cells | 23 | 4·6 |
| Large mononuclear cells | 1 | 0·2 |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 31 | 6·2 | |
| Neutrophilic myelocytes with typical nucleus | 100 | 20·0 | |
| Eosinophilic myelocytes with typical nucleus | 13 | 2·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·2 | |
| Finely granular polynuclear cells | 11 | 2·2 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 222 | 44·4 | 64·6 |
| Large mononuclear cells | 101 | 20·2 | |
| Large hyaline cells | 17 | 3·4 | |
| Coarsely granular basophilic cells | 1 | 0·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 2 | 0·4 | |
| Transitional cells | 1 | 0·2 | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells seen.

EXPERIMENT 33.—*Guinea-pig killed four hours after an intra-peritoneal injection of the above-mentioned toxins.*

| **The blood.** | *Physiological blood.* Leucocytes = 4000 per c.mm. | | | *Pathological blood.* Leucocytes = 6200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 141 | 28·2 | 1120 | 378 | 75·6 | 4650 |
| Coarsely granular polynuclear cells | 117 | 23·4 | 920 | 37 | 7·4 | 434 |
| Small lymphocytes | 155 | 31·0 | 1240 | 26 | 5·2 | 310 |
| Large lymphocytes | 8 | 1·6 | 80 | 9 | 1·8 | 124 |
| Large hyaline cells | 78 | 15·6 | 640 | 46 | 9·2 | 558 |
| Mast cells | 1 | 0·2 | 8 | 2 | 0·4 | 24 |
| Transitional cells | — | — | — | 2 | 0·4 | 24 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was very abundant and turbid.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 441 | 88·2 |
| Coarsely granular polynuclear cells | 43 | 8·6 |
| Small mononuclear cells | 14 | 2·8 |
| Large mononuclear cells | 2 | 0·4 |
| | 500 | |

Large clumps of polynuclear cells, amounting, for example, to 37 and 55 cells respectively, were seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 7 | 2·3 | |
| Neutrophilic myelocytes with typical nucleus | 51 | 17·0 | |
| Eosinophilic myelocytes with typical nucleus | 61 | 20·3 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 10 | 3·3 | |
| Finely granular polynuclear cells | 4 | 1·3 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 122 | 40·6 | 52·2 |
| Large mononuclear cells | 35 | 11·6 | |
| Large hyaline cells | 7 | 2·3 | |
| Coarsely granular basophilic cells | 1 | 0·3 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 2 | 0·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 300 | | |

Thirteen normoblasts and one megaloblast seen while counting 300 cells.

EXPERIMENT 34.—*Guinea-pig killed six hours after an intra-peritoneal injection of the above-mentioned toxins.*

| **The blood.** | *Physiological blood.* Leucocytes=2700 per c.mm. | | | *Pathological blood.* Leucocytes=5100 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 318 | 63·6 | 1728 | 371 | 74·2 | 3774 |
| Coarsely granular polynuclear cells | — | — | — | — | — | — |
| Small lymphocytes | 71 | 14·2 | 378 | 71 | 14·2 | 714 |
| Large lymphocytes | 68 | 13·6 | 378 | 33 | 6·6 | 357 |
| Large hyaline cells | 43 | 8·6 | 243 | 23 | 4·6 | 255 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | 2 | 0·4 | 2 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was very scarce. Cells were very numerous and in large clumps.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 26 | 5·2 |
| Coarsely granular polynuclear cells | 38 | 7·6 |
| Small mononuclear cells | 394 | 78·8 |
| Large mononuclear cells | 42 | 8·4 |
| | 500 | |

Numerous endothelial cells seen while counting 500 leucocytes.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 48 | 4·8 | |
| Neutrophilic myelocytes with typical nucleus | 134 | 13·4 | |
| Eosinophilic myelocytes with typical nucleus | 19 | 1·9 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 2 | 0·2 | |
| Finely granular polynuclear cells | 52 | 5·2 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 496 | 49·6 | 60·0 |
| Large mononuclear cells | 114 | 11·4 | |
| Large hyaline cells | 38 | 3·8 | |
| Coarsely granular basophilic cells | 2 | 0·2 | |
| Finely granular basophilic cells | 3 | 0·3 | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | 1 | 0·1 | |
| | 1000 | | |

Fifteen normoblasts and one megaloblast seen while counting 1000 cells.

EXPERIMENT 35.—*Guinea-pig killed twenty-four hours after an intra-peritoneal injection of the above-mentioned toxins.*

**The blood.**

| | *Physiological blood.* Leucocytes=2900 per c.mm. | | | *Pathological blood.* Leucocytes=3500 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 240 | 48·0 | 1392 | 255 | 51·0 | 1785 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 5 | 3 | 0·6 | 21 |
| Small lymphocytes | 120 | 24·0 | 692 | 124 | 24·8 | 875 |
| Large lymphocytes | 61 | 12·2 | 348 | 78 | 15·6 | 566 |
| Large hyaline cells | 77 | 15·4 | 435 | 39 | 7·8 | 280 |
| Mast cells | 1 | 0·2 | 5 | — | — | — |
| Transitional cells | — | — | — | 1 | 0·2 | 7 |
| | 500 | | | 500 | | |

*Some of the large lymphocytes showed engulfed red cells.* Polychromatophilia was well marked. Three normoblasts and one megaloblast seen while counting 500 cells.

**Peritoneal fluid.**—None present.

| | Per cent. |
|---|---|
| Finely granular polynuclear cells | 88·0 |
| Coarsely granular polynuclear cells | — |
| Small mononuclear cells | 2 |
| Large mononuclear cells | 1·0 |
| Endothelial cells | 9·0 |

The polynuclear cells were very degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 6 | 0·6 | |
| Neutrophilic myelocytes with typical nucleus | 17 | 1·7 | |
| Eosinophilic myelocytes with typical nucleus | 5 | 0·5 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 4 | 0·4 | |
| Finely granular polynuclear cells | 178 | 17·8 | |
| Coarsely granular polynuclear cells | 41 | 4·1 | |
| Small mononuclear cells | 648 | 64·8 | 73·2 |
| Large mononuclear cells | 84 | 8·4 | |
| Large hyaline cells | 16 | 1·6 | |
| Coarsely granular basophilic cells | 1 | 0·1 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Three megaloblasts and one normoblast seen while counting 1000 cells.

EXPERIMENT 36.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the bacillus typhosus.*

**The blood.**

| | *Physiological blood.* Leucocytes=1400 per c.mm. | | | *Pathological blood.* Leucocytes=3100 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 195 | 39·0 | 546 | 198 | 39·6 | 1240 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 2·8 | 1 | 0·2 | 6·2 |
| Small lymphocytes | 266 | 53·2 | 742 | 285 | 57·0 | 1767 |
| Large lymphocytes | 16 | 3·2 | 42 | — | — | — |
| Large hyaline cells | 6 | 1·2 | 14 | 10 | 2·0 | 62 |
| Mast cells | 2 | 0·4 | 5·6 | 2 | 0·4 | 12·4 |
| Transitional cells | 14 | 2·8 | 42 | 4 | 0·8 | 24·8 |
| | 500 | | | 500 | | |

One normoblast seen while counting 500 white cells.

**Peritoneal fluid.** This was abundant.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | — | — | — |
| Coarsely granular polynuclear cells | 1 | 0·2 | — |
| Small mononuclear cells | 450 | 90 | — |
| Large mononuclear cells | 49 | 9·8 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 3 | 0·6 | |
| Neutrophilic myelocytes with typical nucleus | 133 | 26·6 | |
| Eosinophilic myelocytes with typical nucleus | 20 | 4·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 7 | 1·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 244 | 48·8 | 62·0 |
| Large mononuclear cells | 66 | 13·2 | |
| Large hyaline cells | 7 | 1·4 | |
| Coarsely granular basophilic cells | 6 | 1·2 | |
| Finely granular basophilic cells | 1 | 0·2 | |
| Giant cells | 11 | 2·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | 2 | 0·4 | |
| | 500 | | |

No bacilli were seen while counting 500 white cells, and no nucleated red cells were noted.

EXPERIMENT 37.—*Guinea-pig killed one hour after an intra-peritoneal injection of the bacillus typhosus.*

**The blood.**

| | *Physiological blood.* Leucocytes=1800 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes=3400 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 252 | 50·4 | 900 | 252 | 50·4 | 1700 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 3·6 | 1 | 0·2 | 6·8 |
| Small lymphocytes | 83 | 16·6 | 306 | 80 | 16·0 | 544 |
| Large lymphocytes | 149 | 29·8 | 540 | 131 | 26·2 | 884 |
| Large hyaline cells | 15 | 3·0 | 54 | 35 | 7·0 | 238 |
| Mast cells | — | — | — | 1 | 0·2 | 6·8 |
| Transitional cells | — | — | — | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was scarce. Numerous motile bacilli were present. Very many cells were seen lying in clumps.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 255 | 51·0 | 53 |
| Coarsely granular polynuclear cells | 23 | 4·6 | 18 |
| Small mononuclear cells | 208 | 41·6 | 13 |
| Large mononuclear cells | 8 | 1·6 | — |
| Mast cells | 1 | 0·2 | — |
| Transitional cells | 5 | 1·0 | 1 |
| | 500 | | |

Very many of the finely granular polynuclear cells, especially those containing bacilli, were much degenerated. Fair numbers of free bacilli were present.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 28 | 5·6 | |
| Neutrophilic myelocytes with typical nucleus | 107 | 21·4 | |
| Eosinophilic myelocytes with typical nucleus | 14 | 2·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 2 | 0·4 | |
| Finely granular polynuclear cells | 8 | 1·6 | |
| Coarsely granular polynuclear cells | 1 | 0·2 | |
| Small mononuclear cells | 249 | 49·8 | 60·2 |
| Large mononuclear cells | 52 | 10·4 | |
| Large hyaline cells | 31 | 6·2 | |
| Coarsely granular basophilic cells | 6 | 1·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | 1 | 0·2 | |
| Amphophilic cells | 1 | 0·2 | |
| | 500 | | |

Eleven megaloblasts and six normoblasts were seen while counting 500 cells. No bacilli were seen.

EXPERIMENT 38.—*Guinea-pig killed two hours after an intra-peritoneal injection of the bacillus typhosus.*

| **The blood.** | *Physiological blood.* Leucocytes=5500 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes=6900 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 138 | 27·6 | 1485 | 262 | 52·4 | 3588 |
| Coarsely granular polynuclear cells | 10 | 2·0 | 110 | 5 | 1·0 | 69 |
| Small lymphocytes | 338 | 67·6 | 3740 | 216 | 43·2 | 2967 |
| Large lymphocytes | 7 | 1·4 | 55 | 6 | 1·2 | 69 |
| Large hyaline cells | 2 | 0·4 | 22 | 3 | 0·6 | 41 |
| Mast cells | 1 | 0·2 | 11 | — | — | — |
| Transitional cells | 4 | 0·8 | 44 | 8 | 1·6 | 138 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was slightly turbid and abundant. Leucocytes were numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 411 | 82·2 | 14 |
| Coarsely granular polynuclear cells | 17 | 3·4 | 4 |
| Small mononuclear cells | 66 | 13·2 | 4 |
| Large mononuclear cells | 6 | 1·2 | — |
| | 500 | | |

No free bacilli seen. Mast cells were very numerous.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 7 | 1·4 | |
| Neutrophilic myelocytes with typical nucleus | 106 | 21·2 | |
| Eosinophilic myelocytes with typical nucleus | 25 | 5·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 0·6 | |
| Finely granular polynuclear cells | 1 | 0·2 | |
| Coarsely granular polynuclear cells | 2 | 0·4 | |
| Small mononuclear cells | 259 | 51·8 | 67·2 |
| Large mononuclear cells | 77 | 15·4 | |
| Large hyaline cells | 2 | 0·4 | |
| Coarsely granular basophilic cells | 16 | 3·2 | |
| Finely granular basophilic cells | 1 | 0·2 | |
| Giant cells | 1 | 0·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells seen.

EXPERIMENT 38A.—*Guinea-pig killed four hours after an intra-peritoneal injection of the bacillus typhosus.*

**The blood.**

| | *Physiological blood.* Leucocytes = 3200 per c.mm. | | | *Pathological blood.* Leucocytes = 3000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 217 | 43·4 | 1376 | 373 | 74·6 | 2250 |
| Coarsely granular polynuclear cells | 6 | 1·2 | 32 | 4 | 0·8 | 24 |
| Small lymphocytes | 154 | 30·8 | 992 | 63 | 12·6 | 390 |
| Large lymphocytes | 64 | 12·8 | 416 | 30 | 6·0 | 180 |
| Large hyaline cells | 56 | 11·2 | 352 | 30 | 6·0 | 180 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 3 | 0·6 | 19 | — | — | — |
| | 500 | | | 500 | | |

Polychromatophilia was well marked. *About one third of the large hyaline cells were vacuolated.* Blood-platelets numerous.

**Peritoneal fluid.** This was present in fair quantity. No pus or lymph was seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 362 | 72·4 | 7 |
| Coarsely granular polynuclear cells | 3 | 0·6 | — |
| Small mononuclear cells | 124 | 24·8 | — |
| Large mononuclear cells | 10 | 2·0 | 1 |
| Mast cells | 1 | 0·2 | — |
| | 500 | | |

Numerous placards of polynuclear cells were seen agglutinated together. Most of the cells were degenerated. Only few free bacilli were seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 4 | 0·4 | |
| Neutrophilic myelocytes with typical nucleus | 8 | 0·8 | |
| Eosinophilic myelocytes with typical nucleus | 15 | 1·5 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 0·3 | |
| Finely granular polynuclear cells | 162 | 16·2 | |
| Coarsely granular polynuclear cells | 65 | 6·5 | |
| Small mononuclear cells | 542 | 54·2 | 69·0 |
| Large mononuclear cells | 148 | 14·8 | |
| Large hyaline cells | 52 | 5·2 | |
| Coarsely granular basophilic cells | 1 | 0·1 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Two normoblasts were seen while counting 1000 white cells.

EXPERIMENT 39.—*Guinea-pig killed six hours after an intra-peritoneal injection of the bacillus typhosus.*

**The blood.**

| | *Physiological blood.* Leucocytes=3400 per c.mm. | | | *Pathological blood.* Leucocytes=4200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 168 | 33·6 | 1428 | 401 | 80·2 | 2770 |
| Coarsely granular polynuclear cells | 5 | 1·0 | 42 | 2 | 0·4 | 13 |
| Small lymphocytes | 314 | 62·8 | 2646 | 7 | 1·4 | 34 |
| Large lymphocytes | 5 | 1·0 | 42 | 35 | 7·0 | 238 |
| Large hyaline cells | 6 | 1·2 | 42 | 49 | 9·8 | 340 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 168 | 6 | 1·2 | 34 |
| | 500 | | | 500 | | |

**Peritoneal fluid.** This was very abundant. The cells were very numerous.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 356 | 71·2 | — |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 136 | 27·2 | — |
| Large mononuclear cells | 7 | 1·4 | — |
| Mast cells | 1 | 0·2 | — |
| | 500 | | |

No evidence of true phagocytosis was seen. The polynuclear cells were agglutinated into large masses.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 7 | 1·4 | |
| Neutrophilic myelocytes with typical nucleus | 87 | 17·4 | |
| Eosinophilic myelocytes with typical nucleus | 9 | 1·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 5 | 1·0 | |
| Coarsely granular polynuclear cells | 2 | 0·4 | |
| Small mononuclear cells | 275 | 55·0 | 72·6 |
| Large mononuclear cells | 88 | 17·6 | |
| Large hyaline cells | 23 | 4·6 | |
| Coarsely granular basophilic cells | 3 | 0·6 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 1 | 0·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells were seen.

EXPERIMENT 40.—*Guinea-pig killed seventeen hours after an intra-peritoneal injection of the bacillus typhosus.*

**The blood.**

| | *Physiological blood.* Leucocytes = 2300 per c.mm. | | | *Pathological blood.* Leucocytes = 8000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 257 | 51·4 | 1173 | 443 | 88·6 | 7120 |
| Coarsely granular polynuclear cells | 31 | 6·2 | 138 | — | — | — |
| Small lymphocytes | 140 | 28·0 | 644 | 33 | 6·6 | 560 |
| Large lymphocytes | 39 | 7·8 | 184 | 4 | 0·8 | 64 |
| Large hyaline cells | 15 | 3·0 | 69 | — | — | — |
| Mast cells | 1 | 0·2 | 4·6 | — | — | — |
| Transitional cells | 17 | 3·4 | 69 | 17 | 3·4 | 240 |
| Degenerated cells | — | — | — | 3 | 0·6 | 48 |
| | 500 | | | 500 | | |

**Peritoneal fluid** in fair quantity and slightly turbid. No true pus present. Intestines injected.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 489 | 97·8 | 3 |
| Coarsely granular polynuclear cells | 2 | 0·4 | — |
| Small mononuclear cells | 3 | 0·6 | — |
| Large mononuclear cells | 6 | 1·2 | — |
| | 500 | | |

The vast majority of the polynuclear cells were very degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 22 | 3·6 | |
| Neutrophilic myelocytes with typical nucleus | 96 | 16·0 | |
| Eosinophilic myelocytes with typical nucleus | 28 | 4·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 6 | 1·0 | |
| Finely granular polynuclear cells | 5 | 0·8 | |
| Coarsely granular polynuclear cells | 5 | 0·8 | |
| Small mononuclear cells | 336 | 56·0 | 68·1 |
| Large mononuclear cells | 73 | 12·1 | |
| Large hyaline cells | 29 | 4·8 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 600 | | |

One normoblast seen while counting 600 leucocytes.

EXPERIMENT 41.—*Rabbit killed a quarter of an hour after an intra-peritoneal injection of the pneumococcus.*

| **The blood.** | *Physiological blood.* Leucocytes = 3500 per c.mm. | | | *Pathological blood.* Leucocytes = 4400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 220 | 44·0 | 1540 | 266 | 53·2 | 2332 |
| Coarsely granular polynuclear cells | 5 | 1·0 | 35 | 16 | 3·2 | 132 |
| Small lymphocytes | 159 | 31·8 | 1120 | 25 | 5·0 | 220 |
| Large lymphocytes | 63 | 12·6 | 455 | 10 | 12·0 | 528 |
| Large hyaline cells | 48 | 9·6 | 350 | 113 | 22·6 | 1012 |
| Mast cells | 1 | 0·2 | 7 | 7 | 1·4 | 44 |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | 4 | 0·8 | 28 | 13 | 2·6 | 132 |
| | 500 | | | 500 | | |

Polychromatophilia was well marked in very many of the red cells.

**Peritoneal fluid** was very abundant. There were masses of cells present, and many were in clumps.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 61 | 12·2 | — |
| Coarsely granular polynuclear cells | 21 | 4·2 | — |
| Small mononuclear cells | 61 | 12·2 | — |
| Large mononuclear cells | 5 | 1·0 | — |
| Endothelial cells | 352 | 70·4 | 1 |
| | 500 | | |

The endothelial cells were present in enormous numbers.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 11 | 2·2 | |
| Neutrophilic myelocytes with typical nucleus | 168 | 33·6 | |
| Eosinophilic myelocytes with typical nucleus | 4 | 0·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·2 | |
| Finely granular polynuclear cells | 2 | 0·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 239 | 47·8 | 58·4 |
| Large mononuclear cells | 53 | 10·6 | |
| Large hyaline cells | 8 | 1·6 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | 5 | 1·0 | |
| Giant cells | 7 | 1·4 | |
| Transitional cells | — | — | |
| Amphophilic cells | 2 | 0·4 | |
| | 500 | | |

Twenty normoblasts and eight megaloblasts seen while counting 500 white cells.

EXPERIMENT 42.—*Rabbit killed one hour after an intra-peritoneal injection of the pneumococcus.*

**The blood.**

| | *Physiological blood.* Leucocytes = 4600 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes = 4800 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 150 | 30·0 | 1380 | 221 | 44·2 | 2112 |
| Coarsely granular polynuclear cells | 12 | 2·4 | 92 | 20 | 4·0 | 192 |
| Small lymphocytes | 180 | 36·0 | 1656 | 122 | 24·2 | 1152 |
| Large lymphocytes | 70 | 14·0 | 644 | 69 | 13·8 | 672 |
| Large hyaline cells | 68 | 13·6 | 644 | 47 | 9·4 | 432 |
| Mast cells | — | — | — | 2 | 0·4 | 19 |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | 20 | 4·0 | 184 | 19 | 3·8 | 192 |
| | 500 | | | 500 | | |

Blood-platelets were very numerous.

**Peritoneal fluid** present slight in amount. Very few cells seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 400 | 80·0 | — |
| Coarsely granular polynuclear cells | 78 | 15·6 | — |
| Small mononuclear cells | 19 | 3·8 | — |
| Large mononuclear cells | 3 | 0·6 | 1 |
| | 500 | | |

Fair numbers of free cocci seen. One endothelial cell also contained cocci.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 8 | 0·8 | |
| Neutrophilic myelocytes with typical nucleus | 21 | 2·1 | |
| Eosinophilic myelocytes with typical nucleus | 38 | 3·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 5 | 0·5 | |
| Finely granular polynuclear cells | 110 | 11·0 | |
| Coarsely granular polynuclear cells | 50 | 5·0 | |
| Small mononuclear cells | 510 | 51·0 | 72·9 |
| Large mononuclear cells | 219 | 21·9 | |
| Large hyaline cells | 33 | 3·3 | |
| Coarsely granular basophilic cells | 3 | 0·3 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 1 | 0·1 | |
| Transitional cells | — | — | |
| Amphophilic cells | 2 | 0·2 | |
| | 1000 | | |

Thirty-three normoblasts seen while counting 1000 white cells.

EXPERIMENT 43.—*Rabbit killed two hours after an intra-peritoneal injection of the pneumococcus.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes=2400 per c.mm. | | | Leucocytes=2400 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 145 | 29·0 | 696 | 283 | 56·6 | 1344 |
| Coarsely granular polynuclear cells | 17 | 3·4 | 72 | 14 | 2·8 | 72 |
| Small lymphocytes | 227 | 45·4 | 1080 | 118 | 23·6 | 576 |
| Large lymphocytes | 45 | 9·0 | 216 | 27 | 5·4 | 120 |
| Large hyaline cells | 51 | 10·2 | 240 | 58 | 11·6 | 288 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | 15 | 3·0 | 72 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid** present in fair quantity.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 421 | 84·2 | 1 |
| Coarsely granular polynuclear cells | 16 | 3·2 | 1 |
| Small mononuclear cells | 42 | 8·4 | — |
| Large mononuclear cells | 21 | 4·2 | — |
| | 500 | | |

Micro-organisms present in large numbers.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 2 | 0·2 | |
| Neutrophilic myelocytes with typical nucleus | 211 | 21·1 | |
| Eosinophilic myelocytes with typical nucleus | 37 | 3·7 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 2 | 0·2 | |
| Finely granular polynuclear cells | 3 | 0·3 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 558 | 55·8 | 71·7 |
| Large mononuclear cells | 159 | 15·9 | |
| Large hyaline cells | 17 | 1·7 | |
| Coarsely granular basophilic cells | 1 | 0·1 | |
| Finely granular basophilic cells | 3 | 0·3 | |
| Giant cells | 7 | 0·7 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

One hundred and eighteen normoblasts and sixty-three megaloblasts were seen while counting 1000 white cells.

EXPERIMENT 44.—*Rabbit killed four hours after an intra-peritoneal injection of the pneumococcus.*

| **The blood.** | *Physiological blood.* Leucocytes = 2600 per c.mm. | | | *Pathological blood.* Leucocytes = 3600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 190 | 38·0 | 988 | 300 | 60·0 | 2160 |
| Coarsely granular polynuclear cells | 4 | 0·8 | 21 | 4 | 0·8 | 29 |
| Small lymphocytes | 184 | 36·8 | 962 | 98 | 19·6 | 720 |
| Large lymphocytes | 83 | 16·6 | 442 | 49 | 9·8 | 360 |
| Large hyaline cells | 31 | 6·2 | 156 | 39 | 7·8 | 288 |
| Mast cells | — | — | — | 1 | 0·2 | 7 |
| Transitional cells | — | — | — | 1 | 0·2 | 7 |
| Finely basophilic cells | 8 | 1·6 | 52 | 8 | 1·6 | 72 |
| | 500 | | | 500 | | |

**Peritoneal fluid** was seen in slight amount.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 476 | 95·2 | — |
| Coarsely granular polynuclear cells | 3 | 0·6 | — |
| Small mononuclear cells | 20 | 4·0 | — |
| Large mononuclear cells | 1 | 0·2 | — |
| | 500 | | |

One endothelial cell found to be phagocytic. Numerous free cocci seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Neutrophilic myelocytes with typical nucleus | 61 | 12·2 | |
| Eosinophilic myelocytes with typical nucleus | 14 | 2·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 9 | 1·8 | |
| Coarsely granular polynuclear cells | 3 | 0·6 | |
| Small mononuclear cells | 320 | 64·0 | 81·4 |
| Large mononuclear cells | 87 | 17·4 | |
| Large hyaline cells | 4 | 0·8 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | 2 | 0·4 | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

Fifty-two normoblasts and two megaloblasts seen while counting 500 white cells.

EXPERIMENT 45.—*Rabbit killed six hours after an intra-peritoneal injection of the pneumococcus.*

| **The blood.** | *Physiological blood.* Leucocytes = 4100 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes = 4500 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 165 | 33·0 | 1353 | 390 | 78·0 | 3150 |
| Coarsely granular polynuclear cells | 21 | 4·2 | 164 | 4 | 0·8 | 360 |
| Small lymphocytes | 191 | 38·2 | 1558 | 59 | 11·8 | 540 |
| Large lymphocytes | 82 | 16·4 | 656 | 20 | 4·0 | 180 |
| Large hyaline cells | 9 | 1·8 | 82 | 11 | 2·2 | 90 |
| Mast cells | 1 | 0·2 | 8 | 1 | 0·2 | 9 |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | 31 | 6·2 | 246 | 15 | 3·0 | 135 |
| | 500 | | | 500 | | |

Most of the finely granular polynuclear cells were degenerated; *about six contained diplococci.*

**Peritoneal fluid** was very scanty. Fair number of cells seen.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 417 | 83·4 | — |
| Coarsely granular polynuclear cells | 21 | 4·2 | 1 |
| Small mononuclear cells | 40 | 8·0 | — |
| Large mononuclear cells | 21 | 4·2 | — |
| Transitional cells | 1 | 0·2 | — |
| | 500 | | |

Cells were in excellent condition.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Neutrophilic myelocytes with typical nucleus | 115 | 19·1 | |
| Eosinophilic myelocytes with typical nucleus | — | — | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 1 | 0·1 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 427 | 71·1 | 80·4 |
| Large mononuclear cells | 56 | 9·3 | |
| Large hyaline cells | 1 | 0·1 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 600 | | |

No nucleated red cells seen while counting 600 white cells.

EXPERIMENT 46.—*Rabbit killed forty hours after an intra-peritoneal injection of the pneumococcus.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes=3100 per c.mm. | | | Leucocytes=3500 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 235 | 47·0 | 1457 | 361 | 72·2 | 2520 |
| Coarsely granular polynuclear cells | 14 | 2·8 | 93 | — | — | — |
| Small lymphocytes | 209 | 41·8 | 1302 | 74 | 14·8 | 455 |
| Large lymphocytes | 25 | 5·0 | 155 | 20 | 4·0 | 140 |
| Large hyaline cells | 12 | 2·4 | 62 | 26 | 5·2 | 175 |
| Mast cells | 2 | 0·4 | 12 | — | — | — |
| Transitional cells | — | — | — | 6 | 1·2 | 35 |
| Amphophilic cells | 3 | 0·6 | 19 | 4 | 0·8 | 28 |
| Finely basophilic cells | — | — | — | 9 | 1·8 | 70 |
| | 500 | | | 500 | | |

Polychromatophilia was present as usual. Finely granular polynuclear cells markedly degenerated. Eight normoblasts seen while counting 500 leucocytes.

**Peritoneal fluid** present in small amount. Cocci present in masses.

Finely granular polynuclear cells
Coarsely granular polynuclear cells
Small mononuclear cells
Large mononuclear cells
Large hyaline cells

Cells too degenerated to make an accurate count possible.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Neutrophilic myelocytes with typical nucleus | 171 | 17·1 | |
| Eosinophilic myelocytes with typical nucleus | 16 | 1·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | — | — | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 729 | 72·9 | 79·6 |
| Large mononuclear cells | 67 | 6·7 | |
| Large hyaline cells | 11 | 1·1 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | 6 | 0·6 | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Ten normoblasts seen while counting 1000 white cells.

EXPERIMENT 47.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the staphylococcus pyogenes aureus.*

| **The blood.** | *Physiological blood.* Leucocytes = 1500 per c.mm. | | | *Pathological blood.* Leucocytes = 1600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 200 | 40·0 | 600 | 240 | 48·0 | 768 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 3 | 15 | 3·0 | 48 |
| Small lymphocytes | 78 | 15·6 | 240 | 38 | 7·6 | 112 |
| Large lymphocytes | 167 | 33·4 | 495 | 165 | 33·0 | 528 |
| Large hyaline cells | 48 | 9·6 | 150 | 42 | 8·4 | 128 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 6 | 1·2 | ·15 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid** was abundant and somewhat turbid. Very few leucocytes and free cocci were seen.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 20 | 4·0 | 6 |
| Coarsely granular polynuclear cells | 10 | 2·0 | 7 |
| Small mononuclear cells | 458 | 91·6 | 22 |
| Large mononuclear cells | 10 | 2·0 | 2 |
| Transitional cells | 2 | 0·4 | — |
| | 500 | | |

A few free cocci were seen while counting 500 cells, and one or two endothelial cells contained cocci. The cells were in good condition.

**Bone-marrow (femur).**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 71 | 7·1 | |
| Neutrophilic myelocytes with typical nucleus | 113 | 11·3 | |
| Eosinophilic myelocytes with typical nucleus | 22 | 2·2 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 30 | 3·0 | |
| Finely granular polynuclear cells | 20 | 2·0 | |
| Coarsely granular polynuclear cells | 3 | 0·3 | |
| Small mononuclear cells. | 541 | 54·1 | 67·9 |
| Large mononuclear cells | 138 | 13·8 | |
| Large hyaline cells | 29 | 2·9 | |
| Coarsely granular basophilic cells | 10 | 1·0 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 18 | 1·8 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

While counting 1000 white cells, twenty-four normoblasts and seven megaloblasts were seen. No cocci were observed.

EXPERIMENT 48.—*Guinea-pig killed one hour after an intra-peritoneal injection of the staphylococcus pyogenes aureus.*

| **The blood.** | *Physiological blood.* Leucocytes = 2400 per c.mm. | | | *Pathological blood.* Leucocytes = 3000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 140 | 28·0 | 672 | 252 | 50·4 | 1500 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 4·8 | 3 | 0·6 | 18 |
| Small lymphocytes | 179 | 35·8 | 864 | 127 | 25·4 | 750 |
| Large lymphocytes | 27 | 5·4 | 120 | 74 | 14·8 | 450 |
| Large hyaline cells | 145 | 29·0 | 696 | 29 | 7·8 | 240 |
| Mast cells | 3 | 0·6 | 14·4 | — | — | — |
| Transitional cells | 5 | 1·0 | 24 | 5 | 1·0 | 30 |
| | 500 | | | 500 | | |

**Peritoneal fluid** was present in small amount and clear. Numerous leucocytes were seen. Many extra-cellular cocci were found.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 85 | 17·0 | — |
| Coarsely granular polynuclear cells | 48 | 9·6 | 2 |
| Small mononuclear cells | 365 | 73·0 | — |
| Large mononuclear cells | 2 | 0·4 | — |
| | 500 | | |

The cells were in excellent condition.

EXPERIMENT 49.—*Guinea-pig killed two hours after an intra-peritoneal injection of the staphylococcus pyogenes aureus.*

| **The blood.** | *Physiological blood.* Leucocytes = 3500 per c.mm. | | | *Pathological blood.* Leucocytes = 8200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 217 | 43·4 | 1505 | 350 | 70·0 | 5740 |
| Coarsely granular polynuclear cells | 12 | 2·4 | 70 | 1 | 0·2 | 16·4 |
| Small lymphocytes | 182 | 36·4 | 1260 | 95 | 19·0 | 1558 |
| Large lymphocytes | 28 | 5·6 | 210 | 15 | 3·0 | 246 |
| Large hyaline cells | 60 | 12·0 | 420 | 39 | 7·8 | 656 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 1 | 0·2 | 7 | — | — | — |
| | 500 | | | 500 | | |

The platelets were very numerous.

**Peritoneal fluid** was abundant. Very large numbers of leucocytes and masses of cocci in clumps were observed. Many of the cells appeared phagocytic.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 244 | 48·8 | 30 |
| Coarsely granular polynuclear cells | 19 | 3·8 | 8 |
| Small mononuclear cells | 236 | 47·2 | 2 |
| Large mononuclear cells | 1 | 0·2 | 1 |
| | 500 | | |

The cells were mostly in excellent condition, even those which contained cocci. Many cocci were seen in the endothelial cells. Two mast cells were seen while counting 500 leucocytes.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 44 | 4·4 | |
| Neutrophilic myelocytes with typical nucleus | 173 | 17·3 | |
| Eosinophilic myelocytes with typical nucleus | 56 | 5·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 14 | 1·4 | |
| Finely granular polynuclear cells | 6 | 0·6 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 522 | 52·2 | 66·8 |
| Large mononuclear cells | 146 | 14·6 | |
| Large hyaline cells | 21 | 2·1 | |
| Coarsely granular basophilic cells | 11 | 1·1 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 7 | 0·7 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Two normoblasts seen while counting 1000 white cells.

EXPERIMENT 50.—*Guinea-pig killed four hours after an intraperitoneal injection of the staphylococcus pyogenes aureus.*

| **The blood.** | *Physiological blood.* Leucocytes=3100 per c.mm. | | | *Pathological blood.* Leucocytes=4200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 241 | 48·2 | 1488 | 432 | 86·4 | 3612 |
| Coarsely granular polynuclear cells | — | — | — | 2 | 0·4 | 8·4 |
| Small lymphocytes | 152 | 30·4 | 930 | 31 | 6·2 | 252 |
| Large lymphocytes | 41 | 8·2 | 248 | 5 | 1·0 | 42 |
| Large hyaline cells | 64 | 12·8 | 403 | 30 | 6·0 | 252 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 12·4 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid** was very abundant and turbid. Leucocytes were present in enormous masses; the cocci were mostly entirely extra-cellular.

| | Total No. | Per cent. | No phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 419 | 83·8 | 128 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 1 |
| Small mononuclear cells | 55 | 11·0 | — |
| Large mononuclear cells | 22 | 4·4 | 1 |
| Transitional cells | 3 | 0·6 | — |
| | 500 | | |

The vast majority of the finely granular polynuclear cells showed evidence of phagocytosis. Very few free cocci were seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 21 | 4·2 | |
| Neutrophilic myelocytes with typical nucleus | 83 | 16·6 | |
| Eosinophilic myelocytes with typical nucleus | 16 | 3·2 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·2 | |
| Finely granular polynuclear cells | 18 | 3·6 | |
| Coarsely granular polynuclear cells | 2 | 0·4 | |
| Small mononuclear cells | 263 | 52·6 | 67·8 |
| Large mononuclear cells | 76 | 15·2 | |
| Large hyaline cells | 9 | 1·8 | |
| Coarsely granular basophilic cells | 8 | 1·6 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 3 | 0·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells and no cocci were seen.

EXPERIMENT 51.—*Guinea-pig killed seven hours after an intra-peritoneal injection of the staphylococcus pyogenes aureus.*

| **The blood.** | *Physiological blood.* Leucocytes=1800 per c.mm. | | | *Pathological blood.* Leucocytes=4100 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 293 | 58·6 | 1062 | 337 | 67·4 | 2747 |
| Coarsely granular polynuclear cells | 5 | 1·0 | 18 | — | — | — |
| Small lymphocytes | 186 | 37·2 | 666 | 148 | 29·6 | 1230 |
| Large lymphocytes | 1 | 0·2 | 3·6 | 3 | 0·6 | 24·6 |
| Large hyaline cells | 10 | 2·0 | 36 | 10 | 2·0 | 82 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 5 | 1·0 | 18 | 2 | 0·4 | 16·4 |
| | 500 | | | 500 | | |

**Peritoneal fluid** showed enormous masses of leucocytes, of which the majority appeared to be phagocytic.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 431 | 86·2 | 59 |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 15 | 3·0 | 1 |
| Large mononuclear cells | 53 | 10·6 | 2 |
| Transitional cells | 1 | 0·2 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 33 | 6·6 | |
| Neutrophilic myelocytes with typical nucleus | 154 | 30·8 | |
| Eosinophilic myelocytes with typical nucleus | 17 | 3·4 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 9 | 1·8 | |
| Finely granular polynuclear cells | 10 | 2·0 | |
| Coarsely granular polynuclear cells | 1 | 0·2 | |
| Small mononuclear cells | 140 | 28·0 | 47·8 |
| Large mononuclear cells | 99 | 19·8 | |
| Large hyaline cells | 20 | 4·0 | |
| Coarsely granular basophilic cells | 4 | 0·8 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 13 | 2·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells were seen.

EXPERIMENT 52.—*Guinea-pig killed eighteen hours after an intraperitoneal injection of the staphylococcus pyogenes aureus.*

| **The blood.** | *Physiological blood.* Leucocytes=3400 per c.mm. | | | *Pathological blood.* Leucocytes=10,700 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 259 | 51·8 | 1734 | 286 | 57·2 | 6099 |
| Coarsely granular polynuclear cells | 5 | 1·0 | 34 | — | — | — |
| Small lymphocytes | 195 | 39·0 | 1326 | 182 | 36·4 | 3852 |
| Large lymphocytes | 24 | 4·8 | 170 | 12 | 2·4 | 214 |
| Large hyaline cells | 10 | 2·0 | 68 | 14 | 2·8 | 321 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 7 | 1·4 | 34 | 6 | 1·2 | 107 |
| | 500 | | | 500 | | |

The blood-platelets were numerous.

**Peritoneal fluid** was very scanty.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 460 | 92·0 | 151 |
| Coarsely granular polynuclear cells | 1 | 0·2 | — |
| Small mononuclear cells | 12 | 2·4 | — |
| Large mononuclear cells | 27 | 5·4 | 5 |
| | 500 | | |

Many of the finely granular polynuclear cells contained degenerated cocci. There were numerous endothelial cells which were also much degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 25 | 5·0 | |
| Neutrophilic myelocytes with typical nucleus | 110 | 22·0 | |
| Eosinophilic myelocytes with typical nucleus | 16 | 3·2 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 2 | 0·4 | |
| Finely granular polynuclear cells | 62 | 12·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 169 | 33·8 | 48·6 |
| Large mononuclear cells | 74 | 14·8 | |
| Large hyaline cells | 27 | 5·4 | |
| Coarsely granular basophilic cells | 12 | 2·4 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 3 | 0·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

No nucleated red cells seen; no cocci seen.

EXPERIMENT 53.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the normal saline.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes = 1300 per c.mm. | | | Leucocytes = 1000 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 255 | 51·0 | 663 | 287 | 57·4 | 912 |
| Coarsely granular polynuclear cells | — | — | — | 8 | 1·6 | 32 |
| Small lymphocytes | 219 | 43·8 | 572 | 165 | 33·0 | 528 |
| Large lymphocytes | 9 | 1·8 | 26 | 5 | 1·0 | 16 |
| Large hyaline cells | 9 | 1·8 | 26 | 26 | 5·2 | 80 |
| Mast cells | 4 | 0·8 | 10 | 2 | 0·4 | 6 |
| Transitional cells | 4 | 0·8 | 10 | 7 | 1·4 | 16 |
| | 500 | | | 500 | | |

Blood-platelets were numerous.

**Peritoneal fluid** was abundant.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 7 | 1·4 |
| Coarsely granular polynuclear cells | 15 | 3·0 |
| Small mononuclear cells | 471 | 94·2 |
| Large mononuclear cells | 7 | 1·4 |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 70 | 7·0 | |
| Neutrophilic myelocytes with typical nucleus | 179 | 17·9 | |
| Eosinophilic myelocytes with typical nucleus | 25 | 2·5 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 29 | 2·9 | |
| Finely granular polynuclear cells | 25 | 2·5 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 521 | 52·1 | 62·9 |
| Large mononuclear cells | 108 | 10·8 | |
| Large hyaline cells | 31 | 3·1 | |
| Coarsely granular basophilic cells | 9 | 0·9 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 1 | 0·1 | |
| Transitional cells | — | — | |
| Amphophilic cells | 1 | 0·1 | |
| | 1000 | | |

No nucleated red cells were seen.

EXPERIMENT 54.—*Guinea-pig killed one hour after an intra-peritoneal injection of normal saline.*

| **The blood.** | *Physiological blood.* Leucocytes=3100 per c.mm. | | | *Pathological blood.* Leucocytes=4800 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 157 | 31·4 | 961 | 360 | 72·0 | 3456 |
| Coarsely granular polynuclear cells | 2 | 0·4 | 12 | 5 | 1·0 | 48 |
| Small lymphocytes | 171 | 34·2 | 1054 | 116 | 23·2 | 1004 |
| Large lymphocytes | 18 | 3·6 | 124 | 7 | 1·4 | 48 |
| Large hyaline cells | 145 | 29·0 | 899 | 6 | 1·2 | 48 |
| Mast cells | 1 | 0·2 | 6 | — | — | — |
| Transitional cells | 6 | 1·2 | 31 | 6 | 1·2 | 48 |
| | 500 | | | 500 | | |

Blood-platelets were very numerous.

**Peritoneal fluid** was abundant. Very few cells were seen.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 4 | 1·0 |
| Coarsely granular polynuclear cells | 306 | 76·5 |
| Small mononuclear cells | 89 | 22·25 |
| Large mononuclear cells | 1 | 0·25 |
| | 400 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 44 | 6·2 | |
| Neutrophilic myelocytes with typical nucleus | 162 | 23·1 | |
| Eosinophilic myelocytes with typical nucleus | 43 | 6·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 0·4 | |
| Finely granular polynuclear cells | 15 | 2·1 | |
| Coarsely granular polynuclear cells | 2 | 0·2 | |
| Small mononuclear cells | 338 | 48·2 | 57·9 |
| Large mononuclear cells | 68 | 9·7 | |
| Large hyaline cells | 20 | 2·8 | |
| Coarsely granular basophilic cells | 5 | 0·7 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 700 | | |

Two normoblasts seen while counting 700 cells.

EXPERIMENT 55.—*Guinea-pig killed two hours after an intra-peritoneal injection of normal saline.*

| **The blood.** | *Physiological blood.* Leucocytes=3200 per c.mm. | | | *Pathological blood.* Leucocytes=7400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 150 | 37·5 | 1200 | 211 | 42·2 | 3108 |
| Coarsely granular polynuclear cells | 10 | 2·5 | 80 | 55 | 11·0 | 814 |
| Small lymphocytes | 81 | 20·25 | 640 | 212 | 42·4 | 3108 |
| Large lymphocytes | 149 | 37·25 | 1184 | 6 | 1·2 | 74 |
| Large hyaline cells | 10 | 2·5 | 80 | 9 | 1·8 | 148 |
| Mast cells | — | — | — | 2 | 0·4 | 29 |
| Transitional cells | — | — | — | 5 | 1·0 | 74 |
| | 400 | | | 500 | | |

**Peritoneal fluid** present in small amount. Cells were numerous, but did not form clumps.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 156 | 31·2 |
| Coarsely granular polynuclear cells | 157 | 31·4 |
| Small mononuclear cells | 181 | 36·2 |
| Large mononuclear cells | 6 | 1·2 |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 37 | 7·4 | |
| Neutrophilic myelocytes with typical nucleus | 106 | 21·2 | |
| Eosinophilic myelocytes with typical nucleus | 67 | 13·4 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 12 | 2·4 | |
| Finely granular polynuclear cells | 16 | 3·2 | |
| Coarsely granular polynuclear cells | 1 | 0·2 | |
| Small mononuclear cells | 142 | 28·4 | 38·8 |
| Large mononuclear cells | 52 | 10·4 | |
| Large hyaline cells | 32 | 6·4 | |
| Coarsely granular basophilic cells | 9 | 1·8 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | 26 | 5·2 | |
| | 500 | | |

Four normoblasts and two megaloblasts seen while counting 500 cells.

EXPERIMENT 56.—*Guinea-pig killed four hours after an intra-peritoneal injection of normal saline.*

| **The blood.** | *Physiological blood.* Leucocytes = 2700 per c.mm. | | | *Pathological blood.* Leucocytes = 3600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 283 | 56·6 | 1539 | 318 | 63·6 | 2412 |
| Coarsely granular polynuclear cells | 10 | 2·0 | 54 | — | — | — |
| Small lymphocytes | 184 | 36·8 | 999 | 53 | 10·6 | 396 |
| Large lymphocytes | 4 | 0·8 | 21 | 12 | 2·4 | 72 |
| Large hyaline cells | 9 | 1·8 | 54 | 108 | 21·6 | 792 |
| Mast cells | — | — | — | 4 | 0·8 | 28 |
| Transitional cells | 10 | 2·0 | 5·4 | 5 | 1·0 | 36 |
| | 500 | | | 500 | | |

**Peritoneal fluid** present in slight amount. Cells very scanty.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 429 | 85·8 |
| Coarsely granular polynuclear cells | 5 | 1·0 |
| Small mononuclear cells | 59 | 11·8 |
| Large mononuclear cells | 6 | 1·2 |
| Transitional cells | 1 | 0·2 |
| | 500 | |

Cells found to be in good condition.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 35 | 5·8 | |
| Neutrophilic myelocytes with typical nucleus | 166 | 27·6 | |
| Eosinophilic myelocytes with typical nucleus | 11 | 1·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 7 | 1·1 | |
| Finely granular polynuclear cells | 24 | 4·0 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 240 | 40·0 | 50·8 |
| Large mononuclear cells | 65 | 10·8 | |
| Large hyaline cells | 35 | 5·8 | |
| Coarsely granular basophilic cells | 12 | 2·0 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 3 | 0·4 | |
| Transitional cells | 1 | 0·1 | |
| Amphophilic cells | — | — | |
| | 600 | | |

One normoblast seen while counting 600 cells.

EXPERIMENT 57.—*Guinea-pig killed six hours after an intraperitoneal injection of normal saline.*

| **The blood.** | *Physiological blood.* Leucocytes=5100 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes cancelled. Total No. | Per cent. |
|---|---|---|---|---|---|
| Finely granular polynuclear cells | 230 | 46 | 2346 | 283 | 56·6 |
| Coarsely granular polynuclear cells | 6 | 1·2 | 51 | — | — |
| Small lymphocytes | 227 | 45·4 | 2295 | 37 | 7·4 |
| Large lymphocytes | 6 | 1·2 | 51 | 73 | 14·6 |
| Large hyaline cells | 15 | 3·0 | 153 | 95 | 19·0 |
| Mast cells | 4 | 0·8 | 40 | — | — |
| Transitional cells | 12 | 2·4 | 102 | 12 | 2·4 |
| | 500 | | | 500 | |

**Peritoneal fluid** was present in very small amount. Cells were numerous.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 434 | 86·8 |
| Coarsely granular polynuclear cells | — | — |
| Small mononuclear cells | 66 | 13·2 |
| Large mononuclear cells | — | — |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 11 | 1·1 | |
| Neutrophilic myelocytes with typical nucleus | 7 | 0.7 | |
| Eosinophilic myelocytes with typical nucleus | 1 | 0·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 2 | 0·2 | |
| Finely granular polynuclear cells | 328 | 32·8 | |
| Coarsely granular polynuclear cells | 35 | 3·5 | |
| Small mononuclear cells | 432 | 43·2 | 56·3 |
| Large mononuclear cells | 131 | 13·1 | |
| Large hyaline cells | 48 | 4·8 | |
| Coarsely granular basophilic cells | 5 | 0·5 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

No nucleated red cells were seen.

EXPERIMENT 58.—*Guinea-pig killed twenty-four hours after an intra-peritoneal injection of normal saline.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes—2800 per c.mm. | | | Leucocytes—4800 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 152 | 50·66 | 1428 | 214 | 42·8 | 2064 |
| Coarsely granular polynuclear cells | 5 | 1·66 | 56 | 4 | 0·8 | 48 |
| Small lymphocytes | 67 | 22·33 | 616 | 249 | 49·8 | 2400 |
| Large lymphocytes | 27 | 9·0 | 252 | 14 | 2·8 | 144 |
| Large hyaline cells | 48 | 16·0 | 448 | 6 | 1·2 | 48 |
| Mast cells | — | — | — | 5 | 1·0 | 48 |
| Transitional cells | 1 | 0·33 | 8 | 8 | 1·6 | 96 |
| | 300 | | | 500 | | |

Many of the polynuclear (finely granular) cells were seen to be lying in clumps.

**Peritoneal fluid.**—Only a very small quantity was present. Very few leucocytes seen.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 419 | 83·8 |
| Coarsely granular polynuclear cells | 17 | 3·4 |
| Small mononuclear cells | 55 | 11·0 |
| Large mononuclear cells | 9 | 1·8 |
| | 500 | |

Cells were in good condition.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 7 | 0·7 | |
| Neutrophilic myelocytes with typical nucleus | 34 | 3·4 | |
| Eosinophilic myelocytes with typical nucleus | 20 | 2·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 0·3 | |
| Finely granular polynuclear cells | 253 | 25·3 | |
| Coarsely granular polynuclear cells | 44 | 4·4 | |
| Small mononuclear cells | 299 | 29·9 | 50·4 |
| Large mononuclear cells | 205 | 20·5 | |
| Large hyaline cells | 129 | 12·9 | |
| Coarsely granular basophilic cells | 1 | 0·1 | |
| Finely granular basophilic cells | 1 | 0·1 | |
| Giant cells | — | — | |
| Transitional cells | 4 | 0·4 | |
| Amphophilic cells | — | — | |
| | 1000 | | |

No nucleated red cells seen.

EXPERIMENT 59.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of the bacillus coli subsequent to an injection of opium.*

| **The blood.** | *Physiological blood.* Leucocytes=8300 per c.mm. | | | *Pathological blood.* Leucocytes=9800 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 296 | 59·2 | 4897 | 260 | 52·0 | 5096 |
| Coarsely granular polynuclear cells | 15 | 3·0 | 249 | 5 | 1·0 | 98 |
| Small lymphocytes. | 82 | 16·4 | 1328 | 97 | 19·4 | 1862 |
| Large lymphocytes | 14 | 2·8 | 249 | 39 | 7·8 | 784 |
| Large hyaline cells | 83 | 16·6 | 1411 | 98 | 19·6 | 1960 |
| Mast cells | 1 | 0·2 | 16·6 | — | — | — |
| Transitional cells | 9 | 1·8 | 166 | 1 | 0·2 | 18·6 |
| | 500 | | | 500 | | |

**Peritoneal fluid** was present in fair amount. Marked distension of the intestines was observed.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 3 | 0·75 | — |
| Coarsely granular polynuclear cells. | 291 | 72·5 | 155 |
| Small mononuclear cells | 94 | 23·5 | 5 |
| Large mononuclear cells | 12 | 3·0 | 2 |
| | 400 | | |

Endothelial cells were found in large numbers and all were phagocytic.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 41 | 6·8 | |
| Neutrophilic myelocytes with typical nucleus | 109 | 18·1 | |
| Eosinophilic myelocytes with typical nucleus | 70 | 11·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 7 | 1·1 | |
| Finely granular polynuclear cells | 21 | 3·5 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 209 | 34·8 | 46·9 |
| Large mononuclear cells | 73 | 12·1 | |
| Large hyaline cells | 42 | 7·0 | |
| Coarsely granular basophilic cells | 25 | 4·1 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 1 | 0·1 | |
| Transitional cells | 1 | 0·1 | |
| Amphophilic cells | — | — | |
| | 600 | | |

Five normoblasts were seen while counting 600 cells.

EXPERIMENT 60.—*Guinea-pig killed half an hour after an intraperitoneal injection of the above-mentioned bacillus subsequent to an injection of opium.*

| **The blood.** | *Physiological blood.* Leucocytes=8300 per c.mm. | | | *Pathological blood.* Leucocytes=7500 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 336 | 67·2 | 5561 | 380 | 76·0 | 5700 |
| Coarsely granular polynuclear cells | 18 | 3·6 | 332 | 24 | 4·8 | 375 |
| Small lymphocytes | 13 | 2·6 | 249 | 39 | 7·8 | 600 |
| Large lymphocytes | 56 | 11·2 | 913 | 9 | 1·8 | 150 |
| Large hyaline cells | 76 | 15·2 | 1245 | 46 | 9·2 | 675 |
| Mast cells | 1 | 0·2 | 16·6 | — | — | — |
| Transitional cells | — | — | — | 2 | 0·4 | 30 |
| | 500 | | | 500 | | |

**Peritoneal fluid** was present in small amount. Intestines were injected and distended, especially the stomach. Very few cells were seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Endothelial cells | 431 | 86·2 | 145 |
| Finely granular polynuclear cells | 5 | 1·0 | 4 |
| Coarsely granular polynuclear cells | 14 | 2·8 | 12 |
| Small mononuclear cells | 42 | 8·4 | 1 |
| Large mononuclear cells | 8 | 1·6 | 8 |
| | 500 | | |

Micro-organisms were very numerous.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 100 | 10·0 | |
| Neutrophilic myelocytes with typical nucleus | 211 | 21·0 | |
| Eosinophilic myelocytes with typical nucleus | 46 | 4·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 18 | 1·8 | |
| Finely granular polynuclear cells | 151 | 15·1 | |
| Coarsely granular polynuclear cells | 11 | 1·1 | |
| Small mononuclear cells | 219 | 21·9 | 36·9 |
| Large mononuclear cells | 150 | 15·0 | |
| Large hyaline cells | 72 | 7·2 | |
| Coarsely granular basophilic cells | 16 | 1·6 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 6 | 0·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Thirty-seven normoblasts, thirty-three megaloblasts, eleven microblasts, and four gigantoblasts were seen while counting 1000 cells.

EXPERIMENT 61.—*Guinea-pig killed one hour after an intra-peritoneal injection of the above-mentioned bacillus subsequent to an injection of opium.*

**The blood.**

| | *Physiological blood.* Leucocytes=9100 per c.mm. | | | *Pathological blood.* Leucocytes=4600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 253 | 50·6 | 4641 | 324 | 64·8 | 2944 |
| Coarsely granular polynuclear cells | 13 | 2·6 | 273 | 20 | 4·0 | 184 |
| Small lymphocytes | 119 | 23·8 | 3184 | 46 | 9·2 | 414 |
| Large lymphocytes | 24 | 4·8 | 455 | 49 | 9·8 | 460 |
| Large hyaline cells | 89 | 17·8 | 1638 | 60 | 12·0 | 552 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 36·4 | 1 | 0·2 | 9·2 |
| | 500 | | | 500 | | |

[An extra large dose of opium was given in this case, which probably accounts for the severe leucopenia in the pathological blood.]

**Peritoneal fluid** was abundant. Intestines were very injected and greatly distended.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 200 | 50 | 188 |
| Coarsely granular polynuclear cells | 109 | 27·25 | 80 |
| Small mononuclear cells | 76 | 19 | 7 |
| Large mononuclear cells | 15 | 3·75 | 4 |
| | 400 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 35 | 3·5 | |
| Neutrophilic myelocytes with typical nucleus | 97 | 9·7 | |
| Eosinophilic myelocytes with typical nucleus | 41 | 4·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 21 | 2·1 | |
| Finely granular polynuclear cells | 54 | 5·4 | |
| Coarsely granular polynuclear cells | 35 | 3·5 | |
| Small mononuclear cells | 455 | 45·5 | 62·7 |
| Large mononuclear cells | 172 | 17·2 | |
| Large hyaline cells | 36 | 3·6 | |
| Coarsely granular basophilic cells | 33 | 3·3 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 16 | 1·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | 5 | 0·5 | |
| | 1000 | | |

Three megaloblasts and two normoblasts were seen while counting 1000 cells.

EXPERIMENT 62.—*Guinea-pig killed two hours after an intra-peritoneal injection of the above-mentioned bacillus subsequent to an injection of opium.*

| **The blood.** | *Physiological blood.* Leucocytes = 3200 per c.mm. | | | *Pathological blood.* Leucocytes = 6000 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 238 | 47·6 | 1536 | 246 | 49·2 | 2940 |
| Coarsely granular polynuclear cells | 16 | 3·2 | 96 | 21 | 4·2 | 240 |
| Small lymphocytes | 145 | 29·0 | 928 | 63 | 12·6 | 780 |
| Large lymphocytes | 45 | 9·0 | 288 | 99 | 19·8 | 1200 |
| Large hyaline cells | 41 | 8·2 | 256 | 68 | 13·6 | 840 |
| Mast cells | 11 | 2·2 | 64 | 3 | 0·6 | 36 |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | 4 | 0·8 | 25·6 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid** was abundant. Peritoneum was injected and intestines greatly distended.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 227 | 45·4 | 227 |
| Coarsely granular polynuclear cells | 199 | 39·8 | 176 |
| Small mononuclear cells | 65 | 13·0 | 2 |
| Large mononuclear cells | 9 | 1·8 | 5 |
| | 500 | | |

All the polynuclear cells (finely granular) were very much degenerated. Some clumping of the polynuclear cells was observed.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 21 | 2·1 | |
| Neutrophilic myelocytes with typical nucleus | 102 | 10·2 | |
| Eosinophilic myelocytes with typical nucleus | 33 | 3·3 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 12 | 1·2 | |
| Finely granular polynuclear cells | 37 | 3·7 | |
| Coarsely granular polynuclear cells | 27 | 2·7 | |
| Small mononuclear cells | 555 | 55·5 | 68·2 |
| Large mononuclear cells | 127 | 12·7 | |
| Large hyaline cells | 41 | 4·1 | |
| Coarsely granular basophilic cells | 15 | 1·5 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 28 | 2·8 | |
| Transitional cells | — | — | |
| Amphophilic cells | 2 | 0·2 | |
| | 1000 | | |

Five normoblasts were seen while counting 1000 cells.

EXPERIMENT 63.—*Guinea-pig killed four hours after an intra-peritoneal injection of the above-mentioned bacillus subsequent to an injection of opium.*

| **The blood.** | *Pathological blood.* Leucocytes—4600 per c.mm. | | | *Physiological blood.* Leucocytes—6200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 276 | 55·2 | 3410 | 127 | 25·4 | 1150 |
| Coarsely granular polynuclear cells | 27 | 5·4 | 310 | 44 | 8·8 | 414 |
| Small lymphocytes | 70 | 14·0 | 868 | 184 | 36·8 | 1702 |
| Large lymphocytes | 81 | 16·2 | 992 | 46 | 9·2 | 414 |
| Large hyaline cells | 44 | 8·8 | 558 | 91 | 18·2 | 828 |
| Mast cells | — | — | — | 2 | 0·4 | 18·4 |
| Transitional cells | 2 | 0·4 | 24·8 | 3 | 0·6 | 27·6 |
| Finely basophilic cells | — | — | — | 3 | 0·6 | 27·6 |
| | 500 | | | 500 | | |

**Peritoneal fluid** was present in slight amount. Peritoneum was very injected, and the intestines were very greatly distended.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 355 | 71·0 | 355 |
| Coarsely granular polynuclear cells | 107 | 21·4 | 77 |
| Small mononuclear cells | 27 | 5·4 | 5 |
| Large mononuclear cells | 11 | 2·2 | 7 |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 20 | 2·0 | |
| Neutrophilic myelocytes with typical nucleus | 185 | 18·5 | |
| Eosinophilic myelocytes with typical nucleus | 60 | 6·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 20 | 2·0 | |
| Finely granular polynuclear cells | 42 | 4·2 | |
| Coarsely granular polynuclear cells | 25 | 2·5 | |
| Small mononuclear cells | 243 | 24·3 | 55·8 |
| Large mononuclear cells | 315 | 31·5 | |
| Large hyaline cells | 33 | 3·3 | |
| Coarsely granular basophilic cells | 31 | 3·1 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 25 | 2·5 | |
| Transitional cells | — | — | |
| Amphophilic cells | 1 | 0·1 | |
| | 1000 | | |

No nucleated red cells were seen.

EXPERIMENT 64.—*Guinea-pig killed six hours after an intra-peritoneal injection of the above-mentioned bacillus subsequent to an injection of opium.*

| **The blood.** | *Physiological blood.* Leucocytes—8100 per c.mm. | | | *Pathological blood.* Leucocytes—3400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 219 | 43·8 | 3564 | 225 | 56·25 | 1870 |
| Coarsely granular polynuclear cells | 63 | 12·6 | 1053 | 59 | 14·75 | 510 |
| Small lymphocytes | 107 | 21·4 | 1701 | 38 | 9·5 | 340 |
| Large lymphocytes | 76 | 15·2 | 2215 | 48 | 12·0 | 408 |
| Large hyaline cells | 33 | 6·6 | 567 | 30 | 7·5 | 340 |
| Mast cells | 1 | 0·2 | 16·2 | — | — | — |
| Transitional cells | 1 | 0·2 | 16·2 | — | — | — |
| | 500 | | | 400 | | |

**Peritoneal fluid** was abundant. Peritoneum was very much injected and the intestines were markedly distended. Cells agglutinated and bacilli very numerous.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 211 | 52·75 | 211 |
| Coarsely granular polynuclear cells | 162 | 40·50 | 162 |
| Small mononuclear cells | 19 | 4·75 | 5 |
| Large mononuclear cells | 8 | 2·0 | 8 |
| | 400 | | |

Cells present in enormous numbers and showing very large, diffuse clumps. The finely granular polynuclear cells were very much degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 14 | 2·8 | |
| Neutrophilic myelocytes with typical nucleus. | 48 | 9·6 | |
| Eosinophilic myelocytes with typical nucleus | 11 | 2·2 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 9 | 1·8 | |
| Finely granular polynuclear cells | 10 | 2·0 | |
| Coarsely granular polynuclear cells | 5 | 1·0 | |
| Small mononuclear cells | 143 | 28·6 | 66·4 |
| Large mononuclear cells | 189 | 37·8 | |
| Large hyaline cells | 39 | 7·8 | |
| Coarsely granular basophilic cells | 23 | 4·6 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 7 | 1·4 | |
| Transitional cells | 2 | 0·4 | |
| Amphophilic cells | — | — | |
| | 500 | | |

Seven normoblasts and two megaloblasts seen while counting 500 white cells.

EXPERIMENT 65.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of nucleic acid.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes—5800 per c.mm. | | | Leucocytes—6800 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 245 | 49·0 | 2792 | 310 | 62·0 | 4816 |
| Coarsely granular polynuclear cells | 23 | 4·6 | 290 | 18 | 3·6 | 272 |
| Small lymphocytes | 110 | 22·0 | 1276 | 15 | 3·0 | 204 |
| Large lymphocytes | 47 | 9·4 | 522 | 114 | 22·8 | 1564 |
| Large hyaline cells | 73 | 14·6 | 870 | 43 | 8·6 | 728 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 23 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid** abundant, otherwise nothing abnormal observed.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 30 | 6·0 |
| Coarsely granular polynuclear cells | 208 | 41·6 |
| Small mononuclear cells | 198 | 39·6 |
| Large mononuclear cells | 64 | 12·8 |
| | 500 | |

A few clumps of coarsely granular eosinophiles seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 51 | 5·1 | |
| Neutrophilic myelocytes with typical nucleus | 127 | 12·7 | |
| Eosinophilic myelocytes with typical nucleus | 45 | 4·5 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 12 | 1·2 | |
| Finely granular polynuclear cells | 170 | 17·0 | |
| Coarsely granular polynuclear cells | 21 | 2·1 | |
| Small mononuclear cells | 317 | 31·7 | 50·2 |
| Large mononuclear cells | 185 | 18·5 | |
| Large hyaline cells | 26 | 2·6 | |
| Coarsely granular basophilic cells | 2 | 0·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 28 | 2·8 | |
| Transitional cells | — | — | |
| Amphophilic cells | 16 | 1·6 | |
| | 1000 | | |

Four normoblasts and one megaloblast seen while counting 1000 cells.

EXPERIMENT 66.—*Guinea-pig killed one hour after an intraperitoneal injection of nucleic acid.*

| **The blood.** | *Physiological blood.* Leucocytes 3600 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes 4800 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 87 | 17·4 | 612 | 76 | 25·3 | 1200 |
| Coarsely granular polynuclear cells | 5 | 1·0 | 36 | 8 | 2·6 | 144 |
| Small lymphocytes | 61 | 12·2 | 432 | 105 | 35·0 | 1680 |
| Large lymphocytes | 265 | 53·0 | 1908 | 41 | 13·6 | 672 |
| Large hyaline cells | 81 | 16·2 | 576 | 69 | 23·0 | 1104 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 1 | 0·2 | 7 | 1 | 0·3 | 14 |
| | 500 | | | 300 | | |

**Peritoneal fluid** abundant. Very few cells seen. Peritoneum normal appearance.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 256 | 51·2 |
| Coarsely granular polynuclear cells | 61 | 12·2 |
| Small mononuclear cells | 173 | 34·6 |
| Large mononuclear cells | 10 | 2 |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 46 | 4·6 | |
| Neutrophilic myelocytes with typical nucleus | 125 | 12·5 | |
| Eosinophilic myelocytes with typical nucleus | 21 | 2·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 12 | 1·2 | |
| Finely granular polynuclear cells | 6 | 0·6 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 577 | 57·7 | 73·6 |
| Large mononuclear cells | 159 | 15·9 | |
| Large hyaline cells | 37 | 3·7 | |
| Coarsely granular basophilic cells | 1 | 0·1 | |
| Finely granular basophilic cells | 2 | 0·2 | |
| Giant cells | 2 | 0·2 | |
| Transitional cells | 3 | 0·3 | |
| Amphophilic cells | 9 | 0·9 | |
| | 1000 | | |

Twenty-five normoblasts and one megaloblast seen while counting 1000 white cells.

EXPERIMENT 67.—*Guinea-pig killed two hours after an intraperitoneal injection of nucleic acid.*

| **The blood.** | *Physiological blood.* Leucocytes—10,300 per c.mm. | | | *Pathological blood.* Leucocytes—13,200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 116 | 23·2 | 236 | 284 | 47·3 | 625 |
| Coarsely granular polynuclear cells | 247 | 49·4 | 504 | 225 | 37·5 | 495 |
| Small lymphocytes | 121 | 24·2 | 247 | 39 | 6·5 | 85 |
| Large lymphocytes | 1 | 0·2 | 2 | 46 | 7·6 | 105 |
| Large hyaline cells | 1 | 0·2 | 2 | 6 | 1 | 13 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 14 | 2·8 | 30 | — | — | — |
| | 500 | | | 600 | | |

**Peritoneal fluid** abundant. Large numbers of cells present.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 206 | 41·2 |
| Coarsely granular polynuclear cells | 246 | 49·2 |
| Small mononuclear cells | 45 | 9·0 |
| Large mononuclear cells | 3 | 0·6 |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 44 | 4·4 | |
| Neutrophilic myelocytes with typical nucleus | 73 | 7·3 | |
| Eosinophilic myelocytes with typical nucleus | 78 | 7·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 38 | 3·8 | |
| Finely granular polynuclear cells | 36 | 3·6 | |
| Coarsely granular polynuclear cells | 34 | 3·4 | |
| Small mononuclear cells | 451 | 45·1 | 65·1 |
| Large mononuclear cells | 200 | 20·0 | |
| Large hyaline cells | 13 | 1·3 | |
| Coarsely granular basophilic cells | 11 | 1·1 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 10 | 1·0 | |
| Transitional cells | — | — | |
| Amphophilic cells | 12 | 1·2 | |
| | 1000 | | |

Nine normoblasts and four megaloblasts seen while counting 1000 cells.

EXPERIMENT 68.—*Guinea-pig killed four hours after an intra-peritoneal injection of nucleic acid.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes = 2200 per c.mm. | | | Leucocytes = 4230 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 202 | 40·4 | 880 | 236 | 78·6 | 3318 |
| Coarsely granular polynuclear cells | — | — | — | 2 | 0·6 | 25 |
| Small lymphocytes | 112 | 22·4 | 484 | 2 | 0·6 | 25 |
| Large lymphocytes | 13 | 2·6 | 66 | 12 | 8·0 | 336 |
| Large hyaline cells | 170 | 34·0 | 748 | 17 | 11·3 | 462 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 3 | 0·6 | 13 | 2 | 0·6 | 25 |
| | 500 | | | 300 | | |

**Peritoneal fluid** abundant. Enormous masses of cells present in peritoneal fluid.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 470 | 94 |
| Coarsely granular polynuclear cells | 3 | 0·6 |
| Small mononuclear cells | 24 | 4·8 |
| Large mononuclear cells | 3 | 0·6 |
| | 500 | |

Numerous small clumps and one or two large clumps of finely granular polynuclear cells present; many of these cells were very degenerated.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 34 | 3·4 | |
| Neutrophilic myelocytes with typical nucleus | 135 | 13·5 | |
| Eosinophilic myelocytes with typical nucleus | 35 | 3·5 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·1 | |
| Finely granular polynuclear cells | 20 | 2·0 | |
| Coarsely granular polynuclear cells | 2 | 0·2 | |
| Small mononuclear cells | 560 | 56·0 | 74·2 |
| Large mononuclear cells | 182 | 18·2 | |
| Large hyaline cells | 19 | 1·9 | |
| Coarsely granular basophilic cells | 4 | 0·4 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 8 | 0·8 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

One megaloblast and seven normoblasts seen while counting 1000 white cells.

EXPERIMENT 69.—*Guinea-pig killed six hours after an intraperitoneal injection of nucleic acid.*

| **The blood.** | *Physiological blood.* Leucocytes=4800 per c.mm. | | | *Pathological blood.* Leucocytes=8800 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 53 | 10·6 | 528 | 370 | 75·6 | 6688 |
| Coarsely granular polynuclear cells | 75 | 15·0 | 720 | 45 | 9·0 | 792 |
| Small lymphocytes | 127 | 25·4 | 1200 | 10 | 2·0 | 176 |
| Large lymphocytes | 219 | 43·8 | 2112 | 36 | 7·2 | 616 |
| Large hyaline cells | 26 | 5·2 | 240 | 30 | 6·0 | 528 |
| Mast cells | — | — | — | 1 | 0·2 | 17 |
| Transitional cells | — | — | — | — | — | — |
| | 500 | | | 500 | | |

Three normoblasts seen while counting 500 white cells. Marked poikilocytosis and polychromatophilia present. Nearly all the *lymphocytes* have fine *eosinophilic* granules.

Two normoblasts and one megaloblast seen while counting 500 leucocytes, otherwise blood similar to the physiological blood.

**Peritoneal fluid** present in slight amount. Large masses of cells seen.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 393 | 78·6 |
| Coarsely granular polynuclear cells | 25 | 5·0 |
| Small mononuclear cells | 75 | 15·0 |
| Large mononuclear cells | 7 | 1·4 |
| | 500 | |

Finely granular polynuclear cells agglutinated in small placards.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 20 | 2·0 | |
| Neutrophilic myelocytes with typical nucleus | 117 | 11·7 | |
| Eosinophilic myelocytes with typical nucleus | 66 | 6·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 10 | 1·0 | |
| Finely granular polynuclear cells | 7 | 0·7 | |
| Coarsely granular polynuclear cells | 5 | 0·5 | |
| Small mononuclear cells | 515 | 51·5 | 71·5 |
| Large mononuclear cells | 200 | 20·0 | |
| Large hyaline cells | 25 | 2·5 | |
| Coarsely granular basophilic cells | 4 | 0·4 | |
| Finely granular basophilic cells | 3 | 0·3 | |
| Giant cells | 15 | 1·5 | |
| Transitional cells | — | — | |
| Amphophilic cells | 13 | 1·3 | |
| | 1000 | | |

Three gigantoblasts, six megaloblasts, and thirty-five normoblasts seen while counting 1000 white cells.

EXPERIMENT 70.—*Guinea-pig killed twenty-four hours after an intra-peritoneal injection of nucleic acid.*

| **The blood.** | *Physiological blood.* Leucocytes—5400 per c.mm. | | | *Pathological blood.* Leucocytes—7600 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 85 | 17·0 | 918 | 127 | 25·4 | 1900 |
| Coarsely granular polynuclear cells | 3 | 0·6 | 32 | — | — | — |
| Small lymphocytes | 254 | 50·8 | 2754 | 170 | 34·0 | 1384 |
| Large lymphocytes | 67 | 13·4 | 702 | 41 | 8·2 | 608 |
| Large hyaline cells | 91 | 18·2 | 972 | 159 | 31·8 | 2432 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | — | — | — | 3 | 0·6 | 45 |
| | 500 | | | 500 | | |

One normoblast seen while counting 500 leucocytes. No other changes observed in red cells.

**Peritoneal fluid.**—This was found to be scarce.

| | Total No. | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 410 | 82·0 |
| Coarsely granular polynuclear cells | 3 | 0·6 |
| Small mononuclear cells | 87 | 17·4 |
| Large mononuclear cells | — | — |
| | 500 | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 15 | 3·0 | |
| Neutrophilic myelocytes with typical nucleus | 50 | 10·0 | |
| Eosinophilic myelocytes with typical nucleus | 15 | 3·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·2 | |
| Finely granular polynuclear cells | 2 | 0·4 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 302 | 60·4 | 79·8 |
| Large mononuclear cells | 97 | 19·4 | |
| Large hyaline cells | 14 | 2·8 | |
| Coarsely granular basophilic cells | 1 | 0·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 3 | 0·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 500 | | |

Fourteen normoblasts and three megaloblasts seen while counting 500 leucocytes.

EXPERIMENT 71.—*Rabbit killed a quarter of an hour after an intra-peritoneal injection of the streptococcus pyogenes.*

| **The blood.** | *Physiological blood.* Leucocytes = 1600 per c.mm. Total No. | Per cent. | Per c.mm. | *Pathological blood.* Leucocytes = 1700 per c.mm. Total No. | Per cent. | Per c.mm. |
|---|---|---|---|---|---|---|
| Finely granular polynuclear cells | 256 | 51·2 | 816 | 265 | 53·0 | 901 |
| Coarsely granular polynuclear cells | — | — | — | 1 | 0·2 | 3 |
| Small lymphocytes | 115 | 23·0 | 368 | 126 | 25·2 | 425 |
| Large lymphocytes | 72 | 14·4 | 224 | 68 | 13·6 | 238 |
| Large hyaline cells | 43 | 8·6 | 144 | 25 | 5·0 | 85 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 1 | 0·2 | 3 | 3 | 0·6 | 10 |
| Finely basophilic cells | 13 | 2·6 | 48 | 12 | 2·4 | 34 |
| | 500 | | | 500 | | |

No **peritoneal fluid** obtained. Peritoneum appeared to be normal. Very few cells seen and very few cocci.

| | Total No. |
|---|---|
| Finely granular polynuclear cells | — |
| Coarsely granular polynuclear cells | 1 |
| Small mononuclear cells | 8 |
| Endothelial cells | 91 |
| | 100 |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 39 | 3·9 | |
| Neutrophilic myelocytes with typical nucleus | 164 | 16·4 | |
| Eosinophilic myelocytes with typical nucleus | 1 | 0·1 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 34 | 3·4 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 362 | 36·2 | 69·8 |
| Large mononuclear cells | 336 | 33·6 | |
| Large hyaline cells | 43 | 4·3 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | 4 | 0·4 | |
| Giant cells | 14 | 1·4 | |
| Transitional cells | — | — | |
| Amphophilic cells | 2 | 0·2 | |
| | 1000 | | |

Twenty-seven normoblasts, forty-three megaloblasts, and nine gigantoblasts seen while counting 1000 leucocytes.

EXPERIMENT 72.—*Rabbit killed one hour after an intra-peritoneal injection of the streptococcus pyogenes.*

| **The blood.** | *Physiological blood.* Leucocytes = 2800 per c.mm. | | | *Pathological blood.* Leucocytes = 3100 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 288 | 57·6 | 1624 | 314 | 62·8 | 1953 |
| Coarsely granular polynuclear cells | 15 | 3·0 | 84 | 1 | 0·2 | 6 |
| Small lymphocytes | 95 | 19·0 | 532 | 95 | 19·0 | 589 |
| Large lymphocytes | 35 | 7·0 | 196 | 34 | 6·8 | 217 |
| Large hyaline cells | 47 | 9·4 | 252 | 27 | 5·4 | 155 |
| Mast cells | 2 | 0·4 | 11 | 3 | 0·6 | 18 |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | 18 | 3·6 | 112 | 26 | 5·2 | 155 |
| | 500 | | | 500 | | |

Polychromatophilia well marked. One normoblast seen while counting 500 leucocytes.

**Peritoneal fluid** present in fairly large quantity. Peritoneum appeared to be injected. Cocci very abundant.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 486 | 97·2 | — |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 14 | 2·8 | — |
| Large mononuclear cells | — | — | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 21 | 2·1 | |
| Neutrophilic myelocytes with typical nucleus | 233 | 23·3 | |
| Eosinophilic myelocytes with typical nucleus | 8 | 0·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 13 | 1·3 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 172 | 17·2 | 63·7 |
| Large mononuclear cells | 465 | 46·5 | |
| Large hyaline cells | 31 | 3·1 | |
| Coarsely granular basophilic cells | 5 | 0·5 | |
| Finely granular basophilic cells | 17 | 1·7 | |
| Giant cells | 31 | 3·1 | |
| Transitional cells | — | — | |
| Amphophilic cells | 4 | 0·4 | |
| | 1000 | | |

*One hundred and sixty normoblasts, one hundred and eighteen megaloblasts, and fifty-nine gigantoblasts seen while counting* 1000 *white cells.*

EXPERIMENT 73.—*Rabbit killed two hours after an intra-peritoneal injection of the streptococcus pyogenes.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes=2600 per c.mm. | | | Leucocytes=2700 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | — | — | — | 233 | 46·6 | 1323 |
| Coarsely granular polynuclear cells | — | — | — | 6 | 1·2 | 27 |
| Small lymphocytes | — | — | — | 161 | 32·2 | 864 |
| Large lymphocytes | — | — | — | 53 | 10·6 | 297 |
| Large hyaline cells | — | — | — | 42 | 8·4 | 216 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | — | — | — |
| Finely basophilic cells | — | — | — | 5 | 1·0 | 27 |
| | — | | | 500 | | |

**Peritoneal fluid** abundant. Intestinal and parietal peritoneum much injected. Cells present in large clumps.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 380 | 76 | — |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 116 | 23·2 | — |
| Large mononuclear cells | 4 | 0·8 | — |
| | 500 | | |

Cells in good condition.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 8 | 2·6 | |
| Neutrophilic myelocytes with typical nucleus | 72 | 24·0 | |
| Eosinophilic myelocytes with typical nucleus | 3 | 1·0 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 3 | 1·0 | |
| Finely granular polynuclear cells | 3 | 1·0 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 123 | 41·0 | 67·3 |
| Large mononuclear cells | 79 | 26·3 | |
| Large hyaline cells | 6 | 2·0 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | 3 | 1·0 | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 300 | | |

Twenty-three normoblasts and twenty-four megaloblasts seen while 300 white cells were counted.

EXPERIMENT 74.—*Rabbit killed four hours after an intra-peritoneal injection of the streptococcus pyogenes.*

| **The blood.** | *Physiological blood.* Leucocytes=1300 per c.mm. | | | *Pathological blood.* Leucocytes=3200 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 221 | 44·2 | 572 | 364 | 91·0 | 2912 |
| Coarsely granular polynuclear cells | 15 | 3·0 | 39 | 1 | 0·25 | 8 |
| Small lymphocytes | 122 | 24·4 | 312 | 25 | 6·25 | 192 |
| Large lymphocytes | 86 | 17·2 | 221 | 4 | 1·0 | 32 |
| Large hyaline cells | 46 | 9·2 | 117 | 5 | 1·25 | 32 |
| Mast cells | — | — | — | 1 | 0·25 | 8 |
| Transitional cells | 4 | 0·8 | 10 | — | — | — |
| Finely basophilic cells | 6 | 1·2 | 13 | — | — | — |
| | 500 | | | 400 | | |

Polychromatophilia well marked in most of the red cells.

**Peritoneal fluid** abundant. Peritoneum much injected. Leucocytes seen in small clumps.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 478 | 95·6 | — |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 3 | 0·6 | — |
| Large mononuclear cells | 19 | 3·8 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Neutrophilic myelocytes with typical nucleus | 148 | 14·8 | |
| Eosinophilic myelocytes with typical nucleus | 3 | 0·3 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 8 | 0·8 | |
| Coarsely granular polynuclear cells | 4 | 0·4 | |
| Small mononuclear cells | 490 | 49·0 | 77·8 |
| Large mononuclear cells | 288 | 28·8 | |
| Large hyaline cells | 36 | 3·6 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | 10 | 1·0 | |
| Giant cells | 6 | 0·6 | |
| Transitional cells | — | — | |
| Amphophilic cells | 7 | 0·7 | |
| | 1000 | | |

*One hundred and seventy-four normoblasts, fifty-five megaloblasts, and seven gigantoblasts seen while counting* 1000 *white cells.*

EXPERIMENT 75.—*Rabbit killed six hours after an intra-peritoneal injection of the streptococcus pyogenes.*

| **The blood.** | *Physiological blood.* Leucocytes = 4600 per c.mm. | | | *Pathological blood.* Leucocytes = 4900 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 206 | 41·2 | 1886 | 369 | 73·8 | 3626 |
| Coarsely granular polynuclear cells | 10 | 2·0 | 92 | 7 | 1·4 | 49 |
| Small lymphocytes | 112 | 22·4 | 1012 | 43 | 8·6 | 441 |
| Large lymphocytes | 66 | 13·2 | 598 | 26 | 5·2 | 245 |
| Large hyaline cells | 70 | 14·0 | 644 | 53 | 10·6 | 539 |
| Mast cells | 10 | 2·0 | 92 | — | — | — |
| Transitional cells | — | — | — | — | — | — |
| Amphophilic cells | 3 | 0·6 | 27 | — | — | — |
| Finely basophilic cells | 23 | 4·6 | 230 | 2 | 0·4 | 20 |
| | 500 | | | 500 | | |

**Peritoneal fluid** present in small amount. Intestinal and parietal peritoneum injected. Cells very numerous, but not agglutinated.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 476 | 95·2 | — |
| Coarsely granular polynuclear cells | 2 | 0·4 | — |
| Small mononuclear cells | 14 | 2·8 | — |
| Large mononuclear cells | 7 | 1·4 | — |
| Mast cells | 1 | 0·2 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 11 | 1·1 | |
| Neutrophilic myelocytes with typical nucleus | 213 | 21·3 | |
| Eosinophilic myelocytes with typical nucleus | 42 | 4·2 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·1 | |
| Finely granular polynuclear cells | 3 | 0·3 | |
| Coarsely granular polynuclear cells | 1 | 0·1 | |
| Small mononuclear cells | 410 | 41·0 | 67·9 |
| Large mononuclear cells | 269 | 26·9 | |
| Large hyaline cells | 21 | 2·1 | |
| Coarsely granular basophilic cells | — | — | |
| Finely granular basophilic cells | 12 | 1·2 | |
| Giant cells | 7 | 0·7 | |
| Transitional cells | — | — | |
| Amphophilic cells | 10 | 1·0 | |
| | 1000 | | |

Twenty-four normoblasts, forty-five megaloblasts, and eighteen gigantoblasts seen while counting 1000 white cells.

EXPERIMENT 76.—*Rabbit killed twenty-four hours after an intra-peritoneal injection of the streptococcus pyogenes.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes=3000 per c.mm. | | | Leucocytes=3700 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 209 | 41·8 | 1260 | 319 | 63·8 | 2368 |
| Coarsely granular polynuclear cells | 7 | 1·4 | 30 | — | — | — |
| Small lymphocytes | 141 | 28·2 | 840 | 132 | 26·4 | 962 |
| Large lymphocytes | 56 | 11·2 | 330 | 17 | 3·4 | 111 |
| Large hyaline cells | 68 | 13·6 | 420 | 29 | 5·8 | 222 |
| Mast cells | 4 | 0·8 | 24 | 1 | 0·2 | 7 |
| Transitional cells | 5 | 1·0 | 30 | — | — | — |
| Finely basophilic cells | 9 | 1·8 | 60 | 2 | 0·4 | 15 |
| Amphophilic cells | 1 | 0·2 | 6 | — | — | — |
| | 500 | | | 500 | | |

No **peritoneal fluid** obtained.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 399 | 79·8 | — |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 92 | 18·4 | — |
| Large mononuclear cells | 9 | 1·8 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Neutrophilic myelocytes with typical nucleus | 113 | 22·6 | |
| Eosinophilic myelocytes with typical nucleus | 4 | 0·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 4 | 0·8 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 84 | 16·8 | 62·0 |
| Large mononuclear cells | 226 | 45·2 | |
| Large hyaline cells | 38 | 7·6 | |
| Coarsely granular basophilic cells | 4 | 0·8 | |
| Finely granular basophilic cells | 5 | 1·0 | |
| Giant cells | 21 | 4·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | 1 | 0·2 | |
| | 500 | | |

Fifty-one normoblasts, forty-nine megaloblasts, seven gigantoblasts, and one microblast seen while counting 500 white cells.

EXPERIMENT 77.—*Guinea-pig killed a quarter of an hour after an intra-peritoneal injection of a sterile suspension of chalk.*

| **The blood.** | *Physiological blood.* Leucocytes=4800 per c.mm. | | | *Pathological blood.* Leucocytes=5400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 320 | 64·0 | 3072 | 317 | 63·4 | 3402 |
| Coarsely granular polynuclear cells | 24 | 4·8 | 240 | 28 | 5·6 | 324 |
| Small lymphocytes | 71 | 14·2 | 672 | 76 | 15·2 | 810 |
| Large lymphocytes | 30 | 6·0 | 288 | 12 | 2·4 | 108 |
| Large hyaline cells | 54 | 10·8 | 528 | 62 | 12·4 | 648 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 1 | 0·2 | 9 | 5 | 1·0 | 54 |
| | 500 | | | 500 | | |

**Peritoneal fluid** present in very small amount. Cells very scarce.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 6 | 1·5 | — |
| Coarsely granular polynuclear cells | 149 | 37·25 | 83 |
| Small mononuclear cells | 242 | 60·5 | 4 |
| Large mononuclear cells | 3 | 0·75 | 2 |
| | 400 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 23 | 4·6 | |
| Neutrophilic myelocytes with typical nucleus | 25 | 5·0 | |
| Eosinophilic myelocytes with typical nucleus | 41 | 8·2 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | 23 | 4·6 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 270 | 54·0 | 64·6 |
| Large mononuclear cells | 53 | 10·6 | |
| Large hyaline cells | 4 | 0·8 | |
| Coarsely granular basophilic cells | 1 | 0·2 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 9 | 1·8 | |
| Transitional cells | — | — | |
| Amphophilic cells | 1 | 0·2 | |
| | 450 | | |

Two normoblasts seen while counting 450 white cells.

EXPERIMENT 78.—*Guinea-pig killed one hour after an intra-peritoneal injection of a sterile suspension of chalk.*

| **The blood.** | *Physiological blood.* Leucocytes=4150 per c.mm. | | | *Pathological blood.* Leucocytes=4300 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 325 | 65·0 | 2665 | 363 | 72·6 | 3139 |
| Coarsely granular polynuclear cells | 13 | 2·6 | 123 | 9 | 1·8 | 86 |
| Small lymphocytes | 148 | 29·6 | 1230 | 109 | 21·8 | 946 |
| Large lymphocytes | 2 | 0·4 | 16 | 1 | 0·2 | 8 |
| Large hyaline cells | 8 | 1·6 | 82 | 7 | 1·4 | 43 |
| Mast cells | — | — | — | 4 | 0·8 | 34 |
| Transitional cells | 4 | 0·8 | 32 | 7 | 1·4 | 43 |
| | 500 | | | 500 | | |

**Peritoneal fluid** in small amount. Most of the chalk was entangled in the meshes of the great omentum.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 14 | 2·8 | 2 |
| Coarsely granular polynuclear cells | 17 | 3·4 | 7 |
| Small mononuclear cells | 469 | 93·8 | 15 |
| Large mononuclear cells | — | — | — |
| | 500 | | |

Three mast cells also seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 53 | 8·8 | |
| Neutrophilic myelocytes with typical nucleus | 133 | 22·1 | |
| Eosinophilic myelocytes with typical nucleus | 26 | 4·3 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 11 | 1·8 | |
| Finely granular polynuclear cells | 56 | 9·3 | |
| Coarsely granular polynuclear cells | 3 | 0·5 | |
| Small mononuclear cells | 163 | 27·1 | 35·2 |
| Large mononuclear cells | 49 | 8·1 | |
| Large hyaline cells | 67 | 11·1 | |
| Coarsely granular basophilic cells | 39 | 6·5 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 600 | | |

EXPERIMENT 79.—*Guinea-pig killed two hours after an intraperitoneal injection of a sterile suspension of chalk.*

| **The blood.** | *Physiological blood.* Leucocytes=5200 per c.mm. | | | *Pathological blood.* Leucocytes=7150 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 242 | 48·4 | 2496 | 418 | 83·6 | 5964 |
| Coarsely granular polynuclear cells | 38 | 7·6 | 416 | 16 | 3·2 | 213 |
| Small lymphocytes | 103 | 20·6 | 1092 | 17 | 3·4 | 213 |
| Large lymphocytes | 38 | 7·6 | 416 | 25 | 5·0 | 255 |
| Large hyaline cells | 79 | 15·8 | 832 | 21 | 4·2 | 284 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | — | — | — | 3 | 0·6 | 42 |
| | 500 | | | 500 | | |

**Peritoneal fluid** present in fair amount. Chalk enclosed in meshes of great omentum.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 423 | 84·6 | 198 |
| Coarsely granular polynuclear cells | 4 | 0·8 | 2 |
| Small mononuclear cells | 63 | 12·6 | — |
| Large mononuclear cells | 5 | 1·0 | — |
| Transitional cells | 5 | 1·0 | 3 |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 11 | 3·6 | |
| Neutrophilic myelocytes with typical nucleus | 38 | 12·6 | |
| Eosinophilic myelocytes with typical nucleus | 25 | 8·3 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 1 | 0·3 | |
| Finely granular polynuclear cells | — | — | |
| Coarsely granular polynuclear cells | 2 | 0·6 | |
| Small mononuclear cells | 136 | 45·3 | 64·6 |
| Large mononuclear cells | 58 | 19·3 | |
| Large hyaline cells | 18 | 6·0 | |
| Coarsely granular basophilic cells | 11 | 3·6 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 300 | | |

EXPERIMENT 80.—*Guinea-pig killed four hours after an intra-peritoneal injection of a sterile suspension of chalk.*

| **The blood.** | *Physiological blood.* Leucocytes=5600 per c.mm. | | | *Pathological blood.* Leucocytes=6400 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 261 | 52·2 | 2912 | 375 | 75·0 | 4800 |
| Coarsely granular polynuclear cells | 5 | 1·0 | 56 | 3 | 0·6 | 32 |
| Small lymphocytes | 111 | 22·2 | 1232 | 44 | 8·8 | 576 |
| Large lymphocytes | 20 | 4·0 | 224 | 22 | 4·4 | 256 |
| Large hyaline cells | 101 | 20·2 | 1120 | 56 | 11·2 | 704 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 2 | 0·4 | 22 | — | — | — |
| | 500 | | | 500 | | |

**Peritoneal fluid** present in small amount. Large masses of cells present. Particles of chalk entangled in great omentum.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 428 | 85·6 | 26 |
| Coarsely granular polynuclear cells | 25 | 5·0 | 8 |
| Small mononuclear cells | 21 | 4·2 | 8 |
| Large mononuclear cells | 25 | 5·0 | 14 |
| Transitional cells | 1 | 0·2 | — |
| | 500 | | |

One mast cell seen.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 57 | 5·7 | |
| Neutrophilic myelocytes with typical nucleus | 141 | 14·1 | |
| Eosinophilic myelocytes with typical nucleus | 78 | 7·8 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 36 | 3·6 | |
| Finely granular polynuclear cells | 26 | 2·6 | |
| Coarsely granular polynuclear cells | 8 | 0·8 | |
| Small mononuclear cells | 459 | 45·9 | 58·3 |
| Large mononuclear cells | 124 | 12·4 | |
| Large hyaline cells | 60. | 6·0 | |
| Coarsely granular basophilic cells | 9 | 0·9 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 2 | 0·2 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 1000 | | |

Nine normoblasts seen while counting 1000 white cells.

EXPERIMENT 81.—*Guinea-pig killed six hours after an intra-peritoneal injection of a sterile suspension of chalk.*

| **The blood.** | *Physiological blood.* Leucocytes = 4400 per c.mm. | | | *Pathological blood.* Leucocytes = 7700 per c.mm. | | |
|---|---|---|---|---|---|---|
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 241 | 48·2 | 2112 | 374 | 74·8 | 5675 |
| Coarsely granular polynuclear cells | 26 | 5·2 | 220 | 9 | 1·8 | 154 |
| Small lymphocytes | 109 | 21·8 | 960 | 49 | 9·8 | 770 |
| Large lymphocytes | 49 | 9·8 | 440 | 22 | 4·4 | 308 |
| Large hyaline cells | 71 | 14·2 | 616 | 43 | 8·6 | 693 |
| Mast cells | — | — | — | 1 | 0·2 | 15 |
| Transitional cells | 4 | 0·8 | 35 | 2 | 0·4 | 30 |
| | 500 | | | 500 | | |

**Peritoneal fluid** present in large amount. Cells abundant and present in large clumps. Chalk chiefly confined to the great omentum.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 300 | 60 | — |
| Coarsely granular polynuclear cells | 3 | 0·6 | — |
| Small mononuclear cells | 95 | 19 | — |
| Large mononuclear cells | 102 | 20·4 | — |
| | 500 | | |

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 1 | 0·3 | |
| Neutrophilic myelocytes with typical nucleus | 89 | 29·6 | |
| Eosinophilic myelocytes with typical nucleus | 32 | 10·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | — | — | |
| Finely granular polynuclear cells | — | — | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 137 | 45·6 | 57·6 |
| Large mononuclear cells | 36 | 12·0 | |
| Large hyaline cells | 1 | 0·3 | |
| Coarsely granular basophilic cells | 4 | 1·3 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | — | — | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 300 | | |

EXPERIMENT 82.—*Guinea-pig killed twenty-four hours after an intra-peritoneal injection of a sterile suspension of chalk.*

| **The blood.** | *Physiological blood.* | | | *Pathological blood.* | | |
|---|---|---|---|---|---|---|
| | Leucocytes = 4500 per c.mm. | | | Leucocytes = 5600 per c.mm. | | |
| | Total No. | Per cent. | Per c.mm. | Total No. | Per cent. | Per c.mm. |
| Finely granular polynuclear cells | 177 | 35·4 | 1575 | 138 | 27·6 | 1568 |
| Coarsely granular polynuclear cells | 1 | 0·2 | 9 | — | — | — |
| Small lymphocytes | 176 | 35·2 | 1575 | 356 | 71·2 | 3976 |
| Large lymphocytes | 71 | 14·2 | 630 | 4 | 0·8 | 44 |
| Large hyaline cells | 74 | 14·8 | 675 | 2 | 0·4 | 22 |
| Mast cells | — | — | — | — | — | — |
| Transitional cells | 1 | 0·2 | 9 | — | — | — |
| | 500 | | | 500 | | |

**No peritoneal fluid** seen.

| | Total No. | Per cent. | No. phagocytic. |
|---|---|---|---|
| Finely granular polynuclear cells | 390 | 78 | 55 |
| Coarsely granular polynuclear cells | — | — | — |
| Small mononuclear cells | 103 | 20·6 | — |
| Large mononuclear cells | 7 | 1·4 | 1 |
| | 500 | | |

Many endothelial cells also present, all of which were phagocytic to chalk.

**Bone-marrow.**

| | Total No. | Per cent. | |
|---|---|---|---|
| Neutrophilic myelocytes with horse-shoe type of nucleus | 46 | 7·6 | |
| Neutrophilic myelocytes with typical nucleus | 81 | 13·5 | |
| Eosinophilic myelocytes with typical nucleus | 46 | 7·6 | |
| Eosinophilic myelocytes with horse-shoe type of nucleus | 24 | 4·0 | |
| Finely granular polynuclear cells | 29 | 4·83 | |
| Coarsely granular polynuclear cells | — | — | |
| Small mononuclear cells | 274 | 45·6 | 57·6 |
| Large mononuclear cells | 72 | 12·0 | |
| Large hyaline cells | 14 | 2·3 | |
| Coarsely granular basophilic cells | 9 | 1·5 | |
| Finely granular basophilic cells | — | — | |
| Giant cells | 5 | 0·8 | |
| Transitional cells | — | — | |
| Amphophilic cells | — | — | |
| | 600 | | |

*Note.*—Since the paper was read a certain number of experiments which were not then carried out have been added.

*October 17th*, 1905.

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## 12. *On the constitution and mode of action of gastrotoxic serum.*[1]

By Charles Bolton,

From the Pathological Laboratory, University College, London.

### *De sero gastrotoxico.*

Summarium.

In hoc opusculo indagantur constitutio atque actio trium gastrotoxinorum.

(1) Horum præparari potest primum cuniculo immunisando cum cellulis ex caviæ ventriculo.

Postquam cellulæ in cavum abdominale cuniculi injectæ sunt, cuniculi serum sanguinis ad caviam toxicum fit; et hoc serum in cavum abdominale injectum necrosem ac ulcerationem membranæ ventriculi mucosæ efficit.

[1] This paper contains the substance of a preliminary communication, and a continuation of the same, laid before the Royal Society in July, 1904, and February, 1906, respectively.

Hoc sero quoque dissolvuntur in vitro caviæ erythrocyti, ad quam actionem hæmolyticam duo corpora diversa immunisantia pertinent. Ex his alterum e corpore immunisante hæmolytico cuniculi normali sed aucto constat, alterum novum.

Serum gastrotoxicum, insuper, granula protoplasmica lavata cellularum caviæ ventriculi agglutinat, atque cellularum proteidia soluta præcipitat. Similiter efficiuntur proteidia sanguinis seri et illa quoque aut jecoris aut intestini cellularum.

Serum gastrotoxicum cellulas ventriculi normales non dissolvit, sed in his cellulis degeneratio sequitur hyalina.

Cellulis ventriculi additis, materia quæ hanc degenerationem efficit ab sero aufertur; cellulæ aut jecoris aut intestini, tamen, cum hâc materiâ vix conjungere possunt.

Serum hoc gastrotoxicum haud stricte proprium est quod telas alias quam cellulas ventriculi afficit, et quod aliæ telæ toxinum destruere aliquantulum possunt.

Serum, insuper, aut hepatotoxicum aut enterotoxicum, in caviæ ventriculo hæmorrhagiam ac ulcerationem causare potest, atque præcipitat et agglutinat ventriculi proteidia ac illa jecoris aut intestini.

(2) Gastrotoxinum secundum præparatur cuniculo immunisando cum cellulis cuniculi ventriculi. Serum sic præparatum non cuniculum sed caviam afficit. Cellulæ caviæ ventriculi cum hoc cytotoxino in vitro conjungere possunt, sed cuniculi cellulæ haud illud destruunt.

(3) Gastrotoxinum tertium cuniculo immunisando cum cellulis ventriculi humani præparatur. Erythrocytos humanos dissolvit, et proteidia soluta granulaque cellularum ventriculi humani præcipitat atque agglutinat.

Hæ observationes pathogenesem ulcerationis ventriculi humani aliquantulum explicare forsitan possunt.

This research was commenced in 1903 and was undertaken to add, if possible, new facts to our knowledge of cytotoxic action and to throw some light upon the pathology of human gastric ulcer.

In May, 1905, a paper was published by Theohari and Babes (1) on a gastrotoxic serum, but I shall make no further reference to it here, because they have approached the subject, not from the point of view of either cytotoxins or gastric ulcer, but from that of the chemistry of the gastric secretion.

In this communication three gastric cytotoxins will be dealt with, namely:

(1) That obtained by the injection of the stomach-cells of the guinea-pig into the rabbit.

(2) That obtained by the injection of the stomach-cells of the rabbit into the rabbit.

(3) That obtained by the injection of human gastric cells into the rabbit.

The subject will be discussed under the the following headings:

I. Methods.

II. Gastrotoxic serum produced by injecting the rabbit with guinea-pig's stomach-cells.

(*a*) Examination of the serum *in vivo*.

(*b*) Examination of the serum *in vitro*.

(*c*) Specificity of the gastrotoxin.

III. Gastrotoxic serum produced by injecting the rabbit with rabbit's stomach-cells.

IV. Gastrotoxic serum produced by injecting the rabbit with human stomach-cells.

V. Concluding section.

## I. Methods.

*Injection of stomach-cells.*—A guinea-pig which has been previously starved for twenty-four hours is killed by bleeding, the thoracic organs are removed, and a cannula introduced into the thoracic aorta. Normal salt solution is then run through the cannula into the aorta and allowed to issue from the inferior vena cava. In this way the whole of the abdominal organs are washed free from blood. The stomach is cut out, opened, and thoroughly washed. The mucous membrane is then scraped off,

a sterilised knife and a plate being used for this purpose, and ground up with salt solution in a mortar so as to form an emulsion. This emulsion is injected into the peritoneal cavity of a rabbit.

When the rabbit's stomach is used for injection it is treated in exactly the same way.

Pieces of human stomach are obtained from operation cases or immediately after death when possible. In this case the stomach unavoidably contains a variable amount of blood. The rabbits are injected about every ten days, and after four or five injections their blood is found to be highly toxic.

*Bleeding.*— The blood is collected from an artery of the rabbit's ear. It is whipped and centrifugalised and the resulting serum examined *in vivo* and *in vitro.*

In the *in vivo* experiments the serum is injected into the peritoneal cavity of the guinea-pig.

*Examination* in vitro.—The serum is examined with regard to its action upon (1) the red blood corpuscles, (2) the free gastric granules, (3) the soluble proteids of the gastric cells, and (4) the intact gastric cells.

*Hæmolysis.*—A 5 per cent. suspension of guinea-pig's blood corpuscles in salt solution is used for testing the serum.

A known quantity, usually 1 c.c., of the suspension of corpuscles is mixed with diminishing amounts of the serum in a series of test-tubes, the volume of fluid in each tube being made up to the same amount with salt solution. The tubes are incubated for one hour, and then placed in the ice chamber till the next day, when the reading is taken.

*The free gastric granules* are obtained by breaking up the gastric cells in a mortar, making the pulp into an emulsion with salt solution, and centrifugalising slowly.

The resulting fluid contains the suspended granules, which are now brought to the bottom by very rapid centrifugalisation, and washed several times in salt solution until the washings give no precipitate with potassium ferrocyanide and acetic acid.

A few drops of the suspension of granules in salt solution are added to each of a series of tubes containing various dilutions of the gastro-toxic serum. A control of normal saline is prepared, and also a control in which the final washings are added to a small quantity of the serum to make certain that no albumen is

present in them. The tubes are incubated for four or five hours and then examined.

*The soluble proteids* are obtained by making a saline extract of the gastric cells and filtering this through a Berkefeld filter. The gastro-toxic serum is diluted and placed in a series of tubes and to each tube a few drops of the proteid solution are added.

The tubes are incubated for four or five hours and then examined. Controls of normal rabbit's serum and salt solution are also prepared.

*The intact gastric cells* are obtained by scraping off the superficial portion of the mucous membrane of the stomach and suspending the scrapings in salt solution. When the larger pieces of mucous membrane have settled to the bottom, the supernatant fluid is pipetted off and is found to contain free cells and granules in suspension. The cells are washed several times in salt solution to free them from granules and the albuminous fluid in which they float. Three or four drops of the emulsion of cells are added to 2 c.c gastro-toxic serum and the mixture incubated for four or five hours, when the sediment is examined microscopically.

*Admixture of various cells with the serum.*—Various tissues of the body of the guinea-pig have been mixed with the gastro-toxic serum for a certain length of time, usually one hour, in order to find out whether they would combine with the toxin and take it out of solution.

In mixing the various cells with the serum care must be taken that enough cells are present to saturate that fluid, otherwise they will settle to the bottom and a portion of the serum will be unexposed to their action. The intestine-cells are obtained in the same way as described for the stomach. The liver is pounded up and passed through a tea-strainer.

All the tissues and sera used are always obtained fresh on the day of examination. In mixing the various tissues with the serum to test their power of abstracting the hæmolytic factor equal weights of the various organs are mixed with equal volumes of the serum.

Controls are in all cases prepared.

*Microscopical examination.*—Serial sections of parts of more than twenty stomachs have been cut by the paraffin method and were usually stained with hæmatoxylin and eosin.

## II.—Gastrotoxic Serum obtained by injecting the Rabbit with Guinea-pig's Stomach Cells.

### (*a*) *Examination of the serum in vivo.*

The serum is injected into the peritoneal cavity of the guinea-pig. A dose of 10 c.c. usually kills a guinea-pig weighing 200–300 grams within twenty-four hours. Smaller doses (1–5 c.c.) are uncertain in their action. The symptoms are well marked in about half an hour after injection. The animal sits huddled up in a corner and will not move, the temperature falls, and before death general twitchings supervene. With small doses the animal will probably have quite recovered by the following day. All guinea-pigs which are killed by the serum show lesions in their stomachs, and a large number of those which receive small doses and recover show similar lesions. The lesions always occur during the first twenty-four hours after injection.

*Stomach-lesions.*—Patches of necrosis are found, varying in size from that of a pin's head to that of a large area occupying a third or more of the surface of the stomach. These patches are black in colour from altered blood-pigment. The patches are most commonly found near or on one of the curvatures, and they may spread out in transverse streaks along the anterior and posterior walls of the stomach, as if they followed the distribution of the blood-vessels.

After forty-eight hours or less the black patch disappears, leaving a clean and sharply punched out ulcer.

Lesions in other organs are absent and the alimentary canal is either congested or anæmic, but in one or two cases I have found fine capillary hæmorrhages into the mucous membrane of the uterus.

*Microscopic appearance.*—The earliest changes appear to be usually in the gastric cells, which are seen to be diffusely and faintly stained by the eosin, while the nuclei of the interstitial tissue take the hæmatoxylin stain well and show up by contrast.

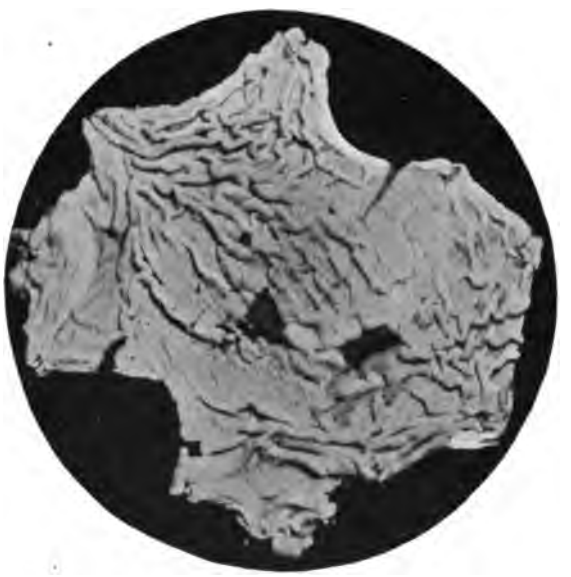
In other cases the earliest change seems to be the appearance of a patch of altered blood-pigment amongst the gastric glands.

The necrosed patches when fully developed are limited to the mucous membrane, and are sharply marked off from the normal tissue. The cells are diffusely stained by the eosin and their

nuclei are unstained; the interstitial tissue nuclei may be stained by the hæmatoxylin or not. The whole patch may look like a brownish coagulated mass in which no structure can be made out. The edges and base of the patch are infiltrated with leucocytes.

An ulcer is formed by the disappearance of the necrosed tissue and its base is infiltrated with leucocytes. The blood in the vessels is very generally normal, but sometimes it is hæmolysed, and may be extravasated in the submucous tissue.

FIG. 27.



Stomach of guinea-pig showing two ulcers. The animal received an injection of 12 c.c. of a weak gastrotoxic serum, and after twenty-four hours it was killed. The serum was prepared by injecting a rabbit with fresh *extract* of guinea-pig's stomach-cells.

EXPLICATIO FIGURÆ.

Caviæ ventriculus, duo ulcera monstrans. Animal interfectum est horas viginti quattuor postquam in cavum abdominale 12 c.cm. seri gastrotoxici injecta erant. Præparatum est serumgastro toxicum in cuniculum injiciendo cellularum extractum caviæ ventriculi.

### (*b*) *Examination of the serum in vitro.*

The gastro-toxin has been found to possess the power of dissolving the guinea-pig's red blood corpuscles, and of pro-

ducing marked changes in the soluble proteids, and also in the protoplasmic granules of the gastric cells of the guinea-pig. It further brings about slight though definite changes in the intact cells themselves.

(1) *Hæmolytic action.*—The normal rabbit's serum is to some extent hæmolytic for the guinea-pig's corpuscles. This action is destroyed by heating the serum to a temperature of 55-60° C. for half an hour and is not restored by the addition of guinea-pig's normal serum (complement).

After a single injection of stomach-cells the hæmolytic power of the rabbit's serum for guinea-pig's corpuscles is found to have considerably increased.

This increase is a true increase of the natural hæmolysin of the rabbit, because its action is destroyed by heat and is not restored by guinea-pig's complement. There may be seen a small amount of laking on reactivating the heated serum with guinea-pig's complement, but this is not to any degree sufficient to account for the total increase of hæmolysin. Later, after further injections it is found that guinea-pig's serum will reactivate the heated immune serum to a considerable extent.

It therefore follows that two distinct hæmolytic immune bodies are called forth by the injection of gastric cells washed free from blood: (1) an increase of the normal hæmolytic immune body of the rabbit which has no complement—ophile affinity corresponding to the guinea-pig's complement; (2) an artificial hæmolytic immune body which is complemented by guinea-pig's serum.

The serum has also the power of agglutinating the red blood corpuscles of the guinea-pig.

(2) *Action upon the protoplasmic granules of the gastric cells.*—On examining the series of tubes containing the diluted serum with granules in suspension, it is found that the fluid contains granules in all stages of agglutination, and that there may be a fine deposit of agglutinated granules at the bottom of the tubes up to a certain dilution; beyond this there is no agglutination; the saline control shows no agglutination; and the control containing the washings shows no precipitate. After the tubes have stood in the ice-chamber till the next day all the agglutinated masses will have settled to the bottom. The blood of a normal rabbit does not agglutinate the granules.

The agglutinin can generally be recognised in the rabbit's blood about fourteen days after the first injection in very small amounts, but sometimes not till after further injections.

*Effects of heat.*—Exposure of the serum to a temperature of 58°–60° C. for half an hour does not affect this agglutinating action. In this respect the agglutinin agrees with those of bacterial origin.

(3) *Action upon the soluble proteids of the gastric cells.*—After one hour's incubation a fine precipitate commences to form in the tubes containing the dilutions of serum together with the solution of gastric proteid. The precipitate forms large flakes and after about four or five hours has settled to the bottom of the tubes in large amount.

Normal rabbit's serum does not precipitate this soluble proteid and the control tube containing salt solution shows no precipitate.

The precipitin is easily recognised about fourteen days after the first injection.

*Effects of heat.*—Exposure to a temperature of 58°–60° C. for half an hour does not diminish the power of the precipitin. Precipitins, as is well known, vary in their power of withstanding heat.

(4) *Action upon the intact gastric cells.*—Neither solution nor agglutination of the cells occurs, but they become more or less hyaline in appearance by exposure to the action of the gastrotoxic serum.

The oxyntic cells are not nearly so much affected as the central cells, the masses of which appear like pieces of floating glass. The granules are obscured and many of the cells look like shadows. The nuclei can usually be seen except when the cells are massed together. The substance producing this hyaline change appears in the blood of the rabbit about five weeks after the first injection, four or five injections having been given in the meanwhile. The substance begins to disappear between three and four months after the first injection in spite of the fact that the animal is receiving injections at regular intervals. Neither normal rabbit's serum nor salt solution produces any such effect upon the gastric cells.

*Effects of heat.*—Exposure to a temperature of 58° C. for half an hour does not destroy the action of the serum, but it may appear to weaken it. It therefore follows that, if this cytotoxin

is of the same nature as hæmolysin, an endocellular complement exists in the cells themselves. The cells themselves cannot be heated to 55° C. because their vitality is destroyed by this procedure, as cell-globulin coagulates at 48°–50° C.

*Removal of gastrolytic factor.* — By saturating the serum with washed gastric cells of the guinea-pig and allowing the mixture to stand for one hour, the gastrolytic factor is removed and the serum is then unable to produce any hyaline change in the cells exposed to its action. The immune body becomes anchored to the cells and on centrifugalisation they carry it out of solution.

(*c*) *Specificity of the gastrotoxin.*—This specificity is tested by ascertaining, (1) whether the gastrotoxin has the power of acting upon other tissues, (2) whether sera formed against other tissues can act upon stomach-cells, (3) whether other tissues can remove the gastrotoxin by combining with it and thus render the serum inactive.

(1) *Action of the gastrotoxin upon other tissues.* — The gastrotoxin has the power, as seen above, of dissolving guinea-pig's blood-corpuscles ; it therefore contains a hæmolytic factor. It also possesses the power of precipitating the proteids of guinea-pig's blood-serum, and it can also agglutinate and precipitate emulsions of liver and intestine cell-granules and proteids. I have not up to the present been able to demonstrate any hyaline change of the liver- or intestine-cells as a result of the action of the gastrolytic factor of the gastrotoxin.

(2) *Action of other sera : hepatotoxic and enterotoxic sera.*— These sera are obtained by injecting the liver- and intestine-cells respectively of the guinea-pig into the rabbit. These two sera on injection into the living guinea-pig produce stomach-lesions which are probably of the same nature as those produced by injecting a hæmolytic serum. The sera are highly hæmolytic in the test-tube and they agglutinate and precipitate gastric granules and soluble proteids as well as liver- and intestine-granules and soluble proteids. I have, however, not yet been able to show any hyaline change in the gastric cells as a result of their action, although more extensive experiments than I have hitherto made may demonstrate such a change.

*Hæmolytic serum*, formed by injecting the blood-corpuscles of the guinea-pig into the rabbit, produces lesions in the guinea-

pig's stomach leading to ulceration. The lesions are secondary to hæmorrhage, and, although usually not so, they may be chiefly limited to the stomach. In other words, the stomach appears to be particularly susceptible to the action of a hæmolytic serum, however that serum has been prepared.

This serum produces no action upon the gastric protoplasm *in vitro.*

(3) *Removal of the gastrotoxin by various tissues. Experiments* in vivo. *Stomach-cells.*—Four experiments have been done. In all the four cases the stomach-cells combined with the gastrotoxin and removed it from the serum so that on injection the serum was inactive. The control animal injected with untreated serum showed in all cases the usual marked lesions.

*Intestine-cells.*—In four cases the intestine cells failed to remove the gastrotoxin, and on injection of the serum so treated lesions were produced which were as extensive as those in the control animals. In three cases the serum was rendered inactive, but the serum was only of low toxic value judging from the slight lesions in the control animals.

*Liver-cells.*—In four cases the liver-cells weakened the action of the serum, but could not destroy it entirely. In one case the gastrotoxin was completely removed, but the serum in this case was only of low toxic value.

*Red blood corpuscles.*—The action of the gastrotoxin was unaffected in three cases and in a fourth this action was weakened, the lesions being less extensive than in the control animal. It is thus evident that stomach-cells alone will invariably render the serum inactive, that other tissues of the body have chemical affinities for *some* of the constituents of the serum, and that they may render the serum less active and even inactive. It follows that the serum itself is not specific for the stomach-cells, although one or more of its constituents may be so to a great extent. These experiments likewise demonstrate the ability of an organ to take up a poison and render it inactive without being itself affected by it. And it thus follows, as has been found to be the case, that large doses of the serum should be necessary to produce the stomach-lesions, since a large part of this serum must be rendered inactive by different tissues of the body.

*Experiments* in vitro. *Hæmolytic factor.*—After treatment with stomach-cells the hæmolytic power of the serum is as high

as it was before such treatment. After treatment, however, with liver-cells and intestine-cells the hæmolytic power of the serum is destroyed.

It seems a remarkable fact that the stomach-cells will not combine with the hæmolysin which is formed in response to their injection, thus showing that they have no chemical affinity for such hæmolysin. It seems from this fact most likely that, when cells are absorbed, side chains having specific affinities for those cells, and which are used in destroying them, are set free, and that other side chains having less affinity for these cells are set free probably in smaller amount, and also side chains having no affinity at all for such cells are set free in smallest amount. In other words, the absorbing cell throws off most of the varieties of side chains or chemical affinities of which it is possessed, the number of each being directly determined by the amount of stimulation given to the particular chemical affinity involved.

I have already stated that the stomach seems to be peculiarly liable to hæmorrhages as the result of the injection of a hæmolytic serum. One would expect this to be the case if the stomach-cells were unable to destoy the factors in the hæmolytic serum giving rise to such hæmorrhage, whereas other organs which could destroy such factors would escape. It seems also clear that the hæmolytic factor of the gastro-toxic serum, although it may be of great importance in assisting to produce the stomach-lesions *in vivo,* is not the only one concerned in so doing; the reasons being, that although previous treatment with stomach-cells will deprive the serum of its action *in vivo,* yet it will not prevent its hæmolytic action *in vitro,* and that previous mixture with liver-cells and intestine-cells, although it deprives the serum of its hæmolytic power *in vitro,* will not with uniform certainty completely destroy its action *in vivo.*

*Gastrolytic factor.*—After exposure of the serum to the action of gastric cells, its power to produce the hyaline change in gastric cells is destroyed. Neither liver- nor intestine-cells, however, can remove this gastrolytic factor, the serum still producing the hyaline change in gastric cells after it has been exposed to the action of liver- and intestine-cells. It may be, therefore, that the gastrolytic factor is specific for the gastric cells, or at any rate specific to a large extent.

### III. Gastrotoxic Serum produced by injecting the Rabbit with Rabbit's Stomach-cells.

The rabbit does not appear to respond very readily to the injection of rabbit's stomach-cells ; however, I have been able to show that it does respond. The serum so obtained produces no effect upon the rabbit itself nor upon any other rabbit, but it is

Fig. 28.

Stomach of guinea-pig, showing a large ulcer situated on the greater curvature and several smaller ones. The animal received an injection of 12 c.c. of gastrotoxic serum, and was almost dead after twenty-four hours, when it was killed. The serum in this case was prepared by injecting a rabbit with *rabbit's* stomach-cells; in the other four cases *guinea-pig's* stomach was used for injection.

Explicatio Figuræ.

Caviæ ventriculus ulcus monstrans magnum et ulcera quædam minora. Animal interfectum est horas viginti quattuor postquam in cavum abdominale 12 c.cm. seri gastrotoxici injecta erant. Præparatum est serum gastrotoxicum in cuniculum injiciendo cellularum extractum cuniculi ventriculi.

toxic for the guinea-pig. My experiments have so far only been conducted *in vivo,* so that I cannot speak with regard to the action of the serum in the test-tube.

*Effects of the serum on injection into the guinea-pig.* — The symptoms and *post-mortem* lesions are identical with those which have been described in the case of the guinea-pig-rabbit gastrotoxic serum. The stomach lesions consist of patches of necrosis and ulceration.

*Previous treatment with rabbit's stomach-cells.*—It might be expected that, since the serum is formed against rabbit's stomach-cells, therefore it should possess affinities corresponding to such cells, and that these cells should render the serum inactive when it is exposed to their action. The rabbit's stomach-cells, however, are quite unable to prevent the serum acting upon guinea-pig's tissues, and it follows therefore that they do not possess affinities corresponding to those of the amboceptor acting upon the guinea-pig's tissues. This is another example of the principle that immune bodies may be set free in response to the injection of a tissue which has no affinities at all for that tissue. Although the rabbit's stomach-cells do not possess affinities corresponding to the immune body active against guinea-pig's tissues, there probably are in this serum immune bodies corresponding to the rabbit's stomach-cells, but that these are saturated by concomitantly formed anti-immune bodies and therefore produce no lesion in the rabbit's stomach.

## IV. Gastrotoxic Serum produced by injecting the Rabbit with Human Stomach-cells.

I have succeeded in showing that it is possible to produce a gastric cytotoxin which is active against human tissues. The gastrotoxic serum so produced is hæmolytic for human blood-corpuscles, and in one case in which I tried it solution of the corpuscles of the monkey also occurred. Of course it is impossible to obtain the human stomach washed free from blood before removal from the body and so it cannot be said that the gastrotoxin itself is hæmolytic, as hæmolysin may have been formed in response to the blood injected. The serum also agglutinates and precipitates emulsions of human gastric granules and soluble proteids, and in one case it acted upon those of the monkey also. Whether hyaline changes are produced in the intact cells I have not yet determined.

## V. Concluding Section.

In response to the injection of gastric cells into an animal the blood of the injected animal shows the presence of a gastric cytotoxin. This gastrotoxin appears to be a complex body and to consist of a hæmolytic factor, a precipitin or precipitins, an agglutinin or agglutinins, and a gastrolytic factor. The fact that a hæmolytic factor is also formed during the process of immunisation against cells washed free from blood has been shown by W. Dungern (2) in the case of ciliated epithelium, and Moxter (3) in the case of spermatozoa.

From my experiments it is clear that this hæmolytic factor is composed of two hæmolysins, at all events in the case of the guinea-pig-rabbit gastrotoxin—(1) an increase of the normal hæmolysin of the rabbit; (2) an artificial hæmolysin, which differs from the former in being complemented by guinea-pig's normal serum after its action has been destroyed by heat. This has an important bearing upon the multiplicity of immune bodies, which view was first advocated by Ehrlich and Morgenroth (4) but which has been recently challenged by Gay (5) and Muir and Browning (6); whether the agglutinin and also the precipitin are composed of separate bodies or whether they act indiscriminately upon all tissues I have not yet determined.

Agglutinins have been described by various observers in the case of different cytotoxins, but I am not aware that they have been separated from precipitins.

The gastrolytic factor does not produce solution of the cells against which it has been formed, as stated by some observers in the case of other cytotoxins, but it undoubtedly produces a hyaline change in these cells and it may be that this substance is specific for these stomach-cells.

The human gastro-toxin is of the same nature as that of lower animals.

Lastly, the importance of these results with regard to the pathology of human gastric ulcer lies in the fact that an animal can elaborate in its blood, as a result of the absorption of the tissues of a similar animal and therefore presumably of its own, a poison which is potentially able to cause necrosis of the mucous membrane of its own stomach.

The reason why lesions do not occur in the animal itself may possibly be that it concomitantly immunises itself against this poison by the formation of an anti-immune body.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*November* 21*st*, 1905.

## 13. *A case of sarcomatous (endotheliomatous) leptomeningitis.*

By ALBERT S. GRÜNBAUM.

CASES of diffuse new growth arising primarily in the cerebro-spinal meninges are uncommon; the last recorded in the 'Transactions' of the Society dates back to 1887, when Drs. Coupland and Pasteur described two cases, one of which the present case resembles in several particulars. Four instances of this condition are mentioned in the German literature. Secondary sarcomatosis is of more frequent occurrence.

I am indebted to Dr. Barrs, under whose care the patient was admitted to the General Infirmary at Leeds, for the use of the clinical notes.

S. P. L—, aged 31 years, married, a warehouseman, was admitted on August 3rd, 1905, complaining of numbness and pain in the left leg, a tight feeling in the abdomen, pain in the back, and dimness of vision.

Family and personal history unimportant.

Present illness commenced five weeks before admission with depression (on account of inability to sing to his children) and dizziness. His doctor advised him to go into the country and he did so without any benefit. Whilst there he had morning vomiting for a week. Subsequently slowness in micturition set in and the left leg became progressively weaker.

On August 16th the condition was as follows: *Eyes*—Slight alternating squint, internal, generally of the left eye. Diplopia in every part of the horizontal field. Optic neuritis. *Arms*—Slight inco-ordination on approximation. *Legs*—Both wasted below the knee. Left nearly powerless. Right fair power. Absence of pain sensation, especially on the outer side. Pin-point not distinguished from blunt pressure of a pencil. *Plantar reflex*—Extensor. No ankle clonus. *Knee-jerks*—Right weaker than left. No rigidity. *Cranial nerves*—Fifth, seventh, ninth, and twelfth, in order. No staccato speech.

August 23rd.—Numbness in finger-tips of both hands. Left leg powerless. On right side ankle clonus and Babinski's sign now obtained. Wasting has increased. Two *quasi*-epileptic attacks.

September 1st—Both legs practically powerless. Knee-jerks

absent. Two fits, at 8.20 a.m and at noon. The latter began in the right arm and on the right side of the face. The head was turned up, back and to the right. Twitching of eyes, nystagmus to right side, the left eye moving more slowly than the right. Rest of body unaffected. Corneæ insensitive during attack. On recovery speech was blurred and unintelligible.

2nd.—Another fit; legs and left arm not affected.

4th.—Some nystagmus to left side.

19th.—In the left eye, in addition to the optic neuritis, there is also advanced retinitis.

26th.—There have not been any more seizures. Patient has become gradually weaker. He died suddenly.

Duration of illness, thirteen weeks.

In none of the cases hitherto published was the diagnosis made during life, nor was it in this instance. A disseminated lesion was expected, but new growth was not anticipated. On other occasions tuberculous or syphilitic meningitis, cerebral tumour, or even hysteria has been the provisional diagnosis, but in every case it was recognised that the symptoms were not typical of the disease surmised.

Lumbar puncture was not done or possibly tumour cells might have been found in the fluid, as suggested by Rindfleisch, who also found the coagulability increased and the albumen in excess of the quantity usually present in non-inflammatory lesions.

The duration of the disease is variable; it may last from one to five months. Considering the nature of the lesion, this period seems short and, compared with its extent, the symptoms relatively slight.

In most instances the patients have been under thirty years of age.

*Autopsy.*—Twenty hours after death, in warm weather. Except in the central nervous system nothing abnormal was discovered. There were no secondary growths elsewhere. Many of the pathological features did not become apparent until the pieces of brain had been preserved in formalin.

On the upper surface of the brain nothing abnormal was seen. The convolutions were not unduly flattened.

Around the base the arachnoid appeared thickened, but what chiefly attracted attention were irregular, opaque, semi-gelatinous, pink outgrowths, sprouting out between the cerebellum and the

pons, and, as was seen later, also encapsuling a portion of the latter, but fitting so closely that it was not detected at the time of the autopsy. On the under-surface of the left lobe of the cerebellum was a flap of tumour about the size of a shilling. Growth could also be traced up into the right lateral ventricle, where it formed some half-dozen grape-like projections which were independent of the choroid plexus. The pial lining of the ventricle appeared thickened. In various portions of and adherent to the cortex, particularly in the more hidden portions like the island of Reil and the inner surface of the uncinate convolution, were numerous lenticular deposits which did not come away on removal of the arachnoid.

In opening the spinal canal the dura mater was cut in the cervical region, and the bulging cord looked so irregular that it was thought to be injured, but this proved not to be the case. The dura mater and the vertebræ were unaffected.

On removal and especially after preservation, it is seen that the whole pia is thickened, less in the upper cervical region, where the nerve-roots are relatively free, than lower down, where many of them are almost hidden from view, particularly where they pass through moniliform accumulations of growth. As in most of the cases already published, the tumour-formation is much thicker on the dorsal than the ventral surface of the cord.

In the lower portion of the dorsal surface of the cervical cord is a large, irregular, hillocky outgrowth, about two segments long and occupying the whole width of the cord. In the lumbar region is a small mound of tumour and between the two run wavy ridges of growth, as well as above and below them, the intermediate area being strewn with small lentil- or bean-shaped eminences. In addition to these irregularities, the whole cord is clothed in a sheet of new growth.

On some of the nerve-roots of the caude equina are small nasturtium-seed-like growths, but the majority have escaped.

In the mid-dorsal and lower lumbar region are a few calcareous plaques.

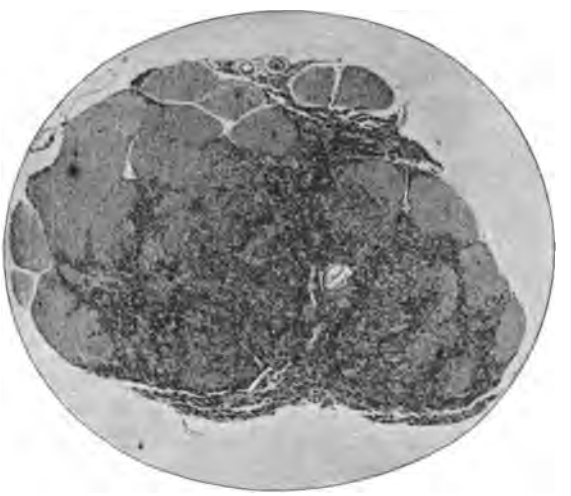
Macroscopically the condition resembles the case described by Coupland and Pasteur more than any other, for an extensive area of growth was visible immediately at the autopsy. In Nonne's case, which is unique, nothing beyond some thickening could be seen with the naked eye, and not until microscope

sections were examined was the pathological diagnosis of new growth made. Here, too, no primary tumour of the central nervous system was detected.

The microscopic nature of the growth presents some features of interest.

Coupland and Pasteur described their specimen as of the simplest cell type, meriting the name of granuloma quite as much as that of round-celled sarcoma. They state definitely that there was no evidence of spindle-cell formation. Bastian's case, which they include, is called an encephaloid sarcoma.

FIG. 29.



**A cross-section of one of the spinal nerves, showing the infiltration of the new growth.**

Nonne describes his case as a perithelioma, without more detailed description of the cells. The distribution of the vascular tumour corresponded to that of the pial vessels. From his photograph it appears possible that two kinds of cell were present.

Coming to my own case, the microscope shows that the growth has penetrated beyond naked-eye limits and has infiltrated normal-looking structures—for instance, the optic nerve.

It is composed of two forms of cell. The larger possesses an oval or ovoid nucleus, slightly larger than an erythrocyte, not staining very intensely and surrounded by only a small quantity

of cytoplasm. These cells are frequently arranged in bands or irregular alveoli. The smaller cell has an intensely staining nucleus, is about half the size of its larger colleague, and has even less cytoplasm. It shows no definite arrangement.

The relative distribution varies in different parts. In the larger and presumably older outgrowths—*e. g.* in the lateral ventricle and on the cerebellum—the large cells predominate, although mixed with smaller cells. Sometimes in the older tumours these larger cells grow out from trabeculæ, like leaves from a branch.

In other places—*e. g.* in the small flat growths on the surface

FIG. 30. FIG. 31.

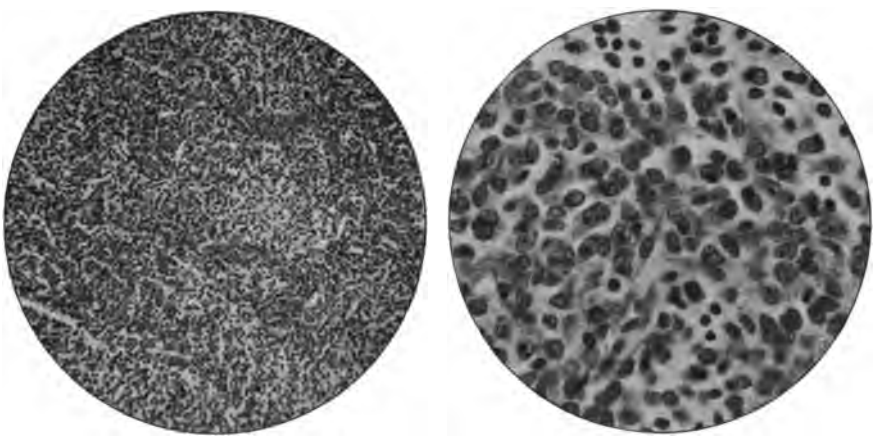


FIG. 30.—A section of the growth in the lateral ventricle, showing the two kinds of cells described in the text, the larger cells exhibiting alveolar arrangement. × 100.

FIG. 31.—The same section as the preceding. × 530.

of the cerebrum and in the optic nerve—the small cell is in the majority.

The tumours are not very vascular, which is rather remarkable considering the pial origin, and in this respect they differ from most of those described by others. Such blood-supply as exists accompanies only the large-celled tissue. In some places hyaline degeneration of the middle coat of the arterioles, already described by Cramer, can be seen.

The growth forms but few metastases in the true sense of the word; its spread is by directly traceable extension along the

lymphatic, interfascicular, or interfibrillar spaces. But in some foci in the cerebellum, consisting only of large cells, this route could not be traced.

As regards the histogenesis, the structure seems to be a mixture of endothelioma and sarcoma, and the question arises as to which is the older.

Lately Ehrlich and Apolant have described mixed tumours resulting from subinoculation of mouse "cancer." This cancer is regarded by v. Hansemann as an endothelioma, so that perhaps the phenomenon observed by Ehrlich and Apolant has a partial counterpart in the present tumour. Since the endotheliomatous cells occur chiefly in the older growths, it would seem that in this instance it was the sarcoma which had stimulated the growth of the endothelioma.

The distinction between the two forms, although pronounced, as may be seen from the figures, is not nearly so marked as in the case of Ehrlich's tumour. Transition forms, such as were noted by Rolleston and O. Grünbaum in the endotheliomata described by them, were not conspicuous and the growth did not arise in a pre-existing mass of connective tissue such as occurs in the parotid or lip.

On the other hand, the condition so far resembles an inflammatory process as to justify the convenient appellation suggested by Rindfleisch, namely sarcomatous meningitis.

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*Coupland and Pasteur.*—'Path. Soc. Trans.,' vol. xxxviii, 1887, p. 26.
*Nonne.*—'Deutsche Zeitschr. f. Nervenheilkunde,' vol. xxi, 1902, p. 396.
*Rindfleisch.*—*Ibid.*, vol. xxvi, 1904, p. 135.
(The two last give references to all the recent literature.)
*Rolleston and Grünbaum,* 'Path. Soc. Trans.,' vol. liv, 1903, p. 353.

*February 20th,* 1906.

## 14. *Doubling of spinal cord.*

By J. M. BERNSTEIN.

THE specimen here described was obtained from a boy aged 16 years, who was admitted to the Westminster Hospital on August

24th, 1904, under the care of Dr. Purves Stewart, suffering from tuberculous meningitis, which resulted in death on August 31st. Previous to the onset of the final illness, some two weeks before admission, there was nothing of importance to note.

At the autopsy there were the usual appearances of tuberculous meningitis in the brain, but the spinal meninges seemed normal. On opening the spinal canal a marked bulging of the membranes in the lumbar region presented itself, this almost completely filling the canal, and at first sight appeared to be due to fluid. But on opening up the dura mater there was found to exist a bifurcation of the cord, beginning in the first lumbar segment, becoming almost complete at the third lumbar segment, where on section to the naked eye there appeared two seemingly complete cords united slightly on their mesial aspects and each showing normal grey and white matter with two anterior and two posterior cornua. Below this the two cords seemed to gradually fuse, the dividing fissure becoming shallower down to the filum terminale, which, though somewhat larger than usual, seemed normal and single.

The cord was fixed in Müller's fluid and then the lower part divided into small segments and paraffin sections made, several sections further being cut of the first lumbar segment to determine if possible the bifurcation of the central canal.

At the upper border of the first lumbar segment the cord was normal, but near the lower border (Fig. 1), although there was only one well-marked and fairly large central canal, the grey commissure was becoming more diffuse and spreading posteriorly. Lower still it had spread anteriorly and posteriorly and a smaller canal appeared antero-laterally to the central canal (Fig. 2), which was here somewhat smaller than the single canal higher up.

In the upper part of the second lumbar segment the cord was divided into almost complete halves by the prolongation of the median septa (Fig. 3), each half exhibiting a canal (or as it seemed in some sections the outer portion of a central canal in the process of division) very near to the median line, a complete anterior and posterior cornu with associated nerve bundles and well-marked motor cells, and internally a portion of grey matter (grey commissure), which extended somewhat diffusely on to the bisecting pia mater. Descending farther, the two

canals became complete and diverged towards the centre of each half, without, however, completely reaching this point. The portion of grey commissure in each spread itself out somewhat into the form of an anterior and posterior cornu (Fig. 4) drawing away from the dividing pia mater from which it became separated by a layer of white matter. Meanwhile the separation of the two halves became more complete and an anterior fissure and a less perfect posterior septum appeared in each half. The anterior fissures at first were situated close to and never diverged far from the original antero-mesial fissure, which did not bifurcate but became continuous with the fissure between the two cords.

In the third lumbar segment there resulted two cords completely separated, each with an antero- and postero-median septum, a central canal, and four cornua. But whilst in the outer cornua, which were better developed and shaped than the inner, the nerve-cells appeared normally grouped, only in a few sections could any nerve-cells whatsoever be made out in the inner cornua, and these indeed exceedingly scanty and of small size (Figs. 5 and 6). And further, the nerve roots in every case seemed associated with the outer cornua only. The two cords were placed as if their anterior poles had been rotated towards the mesial line, so that the antero-mesial fissures converged towards the middle line. The grey matter of the "inner cornua" was very diffuse and much broken up by strands of white matter, and on one side showed what seemed to be a well-marked substantia gelatinosa capping the pseudo-posterior horn.

Below this level the two cords gradually fused again, but not in so symmetrical a manner as they had separated. The adjacent anterior cornua united first (Fig. 7) one posterior septum together with some white matter separating the two inner posterior cornua, whilst the two antero-mesial septa were present and the two canals remained.

Descending lower, the two antero-mesial fissures fused into a single fissure, bifurcated at its termination, and one half of the cord rapidly approached the normal, its central canal remaining as the true central canal of the rest of the cord and its inner posterior cornu merging into grey commissure again. But the other half remained abnormal to the end, the true anterior cornu, with its well-marked nerve-cells being demarcated by a

constriction (Fig. 8) at the site of its former antero-mesial fissure, at which point an ill-developed central canal separated it from an irregular diffuse mass of grey matter which helped to form the grey commissure. The posterior cornu of this half was ill-defined (Fig. 9) and the posterior roots scattered, being more numerous but smaller than the accumulated and normally situated roots of the opposite side.

In the sacral region there could still be seen a small remnant of the additional canal on the antero-mesial side of the still slightly constricted anterior cornu, a second postero-mesial septum, and scattered posterior roots, the whole forming an asymmetrical cord (Figs. 10, 11).

At first this appeared to be a true and complete reduplication of the lumbar cord with two central canals, derived by bifurcation of the single central canal, which in the sections appeared markedly larger than the two immediately below it. But seeing that the nerve-cells are for the most part, if not entirely, situated in the outer cornua, which were the true anterior cornua of the undivided cord, and that the posterior roots are associated with the outer cornua also, it seems more probable that the so-called inner cornua are merely masses of expanded grey matter, which higher up formed the grey commissure, and which have become separated by prolongation of the fissures, a layer of white matter ultimately separating each portion from the pia mater completely dividing the cord. This is further supported by the more minute examination of these inner cornua, which are then seen to be very much diffused, and cut up by much white matter.

Bruce, M'Donald and Pirie[1] review all the cases hitherto described, viz. 35 cases collected by Steiner and 5 additional ones. Of the 35 they eliminate 12 as being merely split cords, and 13 as artefacts, leaving 10 cases of true doubling. These with the remaining cases they divide into 9 undoubted and 6 probable examples of doubling. Of these 7 were associated with spina bifida. In seven the bony canal was normal, and of these 2 occurred in fœtuses, the ages of the remaining 5 being from 31 to 76 years and all were in the lumbar region. From the diagrams given, it would appear that the cases of v. Recklinghausen, Theodor, and Steiner and Bruce's own first case are

[1] 'Review of Psychiatry and Psychology,' Nov., 1904, p. 6.

## DESCRIPTION OF FIGURES.

The figures have been drawn to scale with the aid of the Edinger projection apparatus, with the kind assistance of Dr. Purves Stewart. The levels denoted are approximate.

FIG. 1.—Lower end of first lumbar segment. The cord is single, with a large central canal, but there is some slight deformity of the grey commissure on the left side posteriorly.

FIG. 2.—A little lower than Fig. 1. The grey commissure is increased in extent and shows anterior and posterior outgrowths. A smaller canal is present on the left side, anterior to the central one, which here is much smaller than in Fig. 1. The nerve-roots are normally situated.

FIG. 3.—Level of second lumbar segment. The anterior and posterior septa have almost united and split the grey commissure into two ill-defined masses, each possessing apparently a portion of the central canal, which in serial sections appeared to draw away from the median line. Anterior cornual cells and nerve-roots normally situated.

FIG. 4.—Second lumbar segment at a lower level than Fig. 3. The two halves are separated by pia mater. An antero-median septum is seen on each side. Two complete canals are present and the grey matter is taking on the shape of anterior and posterior cornua and is separated from the dividing pia mater by white matter. On the left side, in the new posterior cornu, a few very small nerve-cells are seen near the central canal, but otherwise the nerve-cells are in the original anterior cornua.

FIG. 5.—Upper part of third lumbar segment. The cords are completely separated. No nerve-roots are associated with the apposed cornua.

FIG. 6.—Third lumbar segment. Two almost complete cords are seen. The outer portions of each, however, are much more complete and better developed than the inner, in which only very few ill-developed nerve-cells are seen. Two central canals are present and an antero-mesial septum is present in each. The cords are placed as if their anterior poles had been rotated inwards. On the right side what appears to be a well-marked substantia gelatinosa is seen capping the inner posterior cornu.

FIG. 7.—Fourth lumbar segment. The two apposed portions of grey matter have fused anteriorly, the posterior portions still remaining apart. The two posterior cornua on the right side are somewhat ill-defined. The two canals are symmetrical. A few nerve-cells are seen in the fused anterior portions and the nerve-roots are still associated with the outer cornua.

FIG. 8.—Fifth lumbar segment. The left half is almost normal, with a well-marked anterior and posterior cornu, and its central canal has become the true central canal of the rest of the cord. The right half is still abnormal, its anterior cornu, with well-marked nerve-cells, being demarcated by a constriction in which is seen the remnant of the central canal of this half at the site of its original median septa, traces of which are still present. The posterior horn is somewhat diffused, and the posterior roots are widely scattered, in contrast to the accumulated and larger roots of the opposite side. The antero-median fissure is bifurcated at its termination.

FIGS. 9–11.—Sacral region. The asymmetry becomes less marked, but does not entirely disappear. The antero-median fissure and posterior septum become normal. There is in the lowest sacral region (Fig. 11) still a trace of an additional canal on the right side. The right posterior roots remain scattered and the posterior horn somewhat diffuse, a constriction still separating it from the anterior cornu at a point opposite to a depression in the pia, representing the postero-median septum of this side.

FIG. 32.

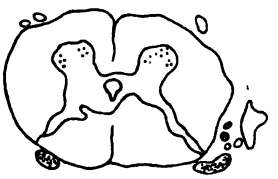

Fig. 1.

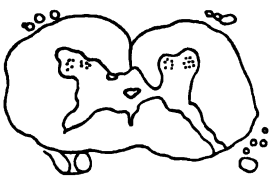

Fig. 2.

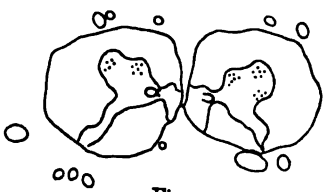

Fig. 3.

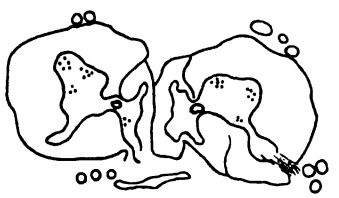

Fig. 4.

Fig. 5.

Fig. 6.

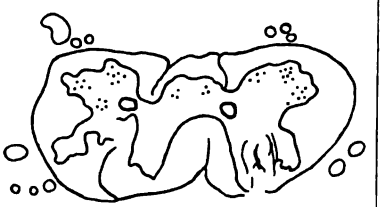

Fig. 7.

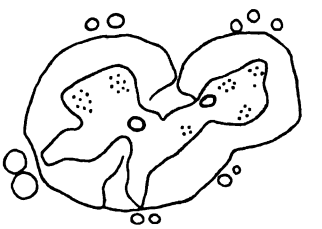

Fig. 8.

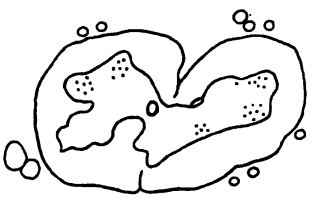

Fig. 9.

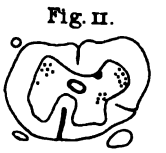

Fig. 11.

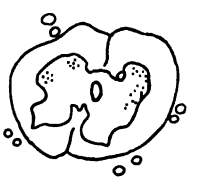

Fig. 10.

examples of complete division and resemble the case here described. Sulzer's case shows diffusion and spreading of the grey commissure, and Miura's shows division of the grey commissure, etc., but without complete division of the white matter. The second case of Bruce, M'Donald and Pirie appears to be an extension of the grey commissure posteriorly into two processes which resemble additional posterior cornua and become separated from the middle line by columns of white matter; and although the anterior fissure bifurcates slightly, the cord is far from approaching complete division.

The outer cornua in all the cases were much better developed and apparently the posterior roots were always associated with the outer cornua and the motor cells with the outer anterior cornua, although occasionally a few appeared in the inner cornua. It would appear therefore that none of these cases are examples of true and complete doubling.

*February 20th*, 1906.

## 15. *Phlegmonous gastritis.*

By J. M. Bernstein.

The specimen was obtained from the body of a woman aged 65 years, who was admitted to the Westminster Hospital under the care of Dr. Hebb, to whose usual kindness I am indebted for permission to publish the case and also for much valuable assistance.

There was a history of a sudden onset of acute illness four days previously, with rigors, and two days later vomiting set in and persisted.

On admission the tongue was dry and reddish-brown, the abdomen much distended and tense but not tender, although the legs were drawn up. There were no other marked physical signs, the mind was clear, the hands dark red or purple but not cold, and the aspect was renal; temperature 101°.

The vomiting was not marked after admission, and a diagnosis of peritonitis was the most that could be made. Death occurred at 2 a.m., ten hours after admission and about five days after the

onset, from septicæmia. Her friends supplied a history of chronic alcoholism and of a drinking bout immediately preceding the final illness.

The necropsy made twelve hours after death revealed the following appearances: Body warm, skin spotted with purple spots and blotches of varying size, abdomen distended, mucosa of tongue and fauces of a dusky purple, and a few suppurative foci in the slightly enlarged tonsils. Œsophagus normal. On opening the abdomen an acute suppurative peritonitis presented

FIG. 33.

Vertical sections showing the thickness of the purulent infiltration of the submucous coat referred to. The upper figure is from the cardiac end, the lower from the pyloric; in the latter the lesion ceases abruptly at the pylorus itself. In the upper of the figures the mucosa lies inferiorly; in the lower, superiorly. (Nat. size.)

itself, the bulk of the slimy pus showing in the subdiaphragmatic region. Numerous old peritoneal adhesions around the liver, pancreas, stomach, and spleen.

The stomach was very large, the walls thick and soft, and the mucosa much swollen from inflammatory œdema, presenting the appearance of an acute gastritis, with fine injection of the capillary vessels, leading to a bright red coloration, which was more marked on the posterior surface of the fundus. No ulceration could be made out at any part of the mucosa, but at the fundus minute white purulent foci showed beneath the surface,

in marked contrast to the deeply congested mucosa. More remarkable, however, was the submucosa. This was the seat of a diffuse suppurative infiltration throughout its whole extent, though more especially towards the pylorus. Here the wall was so thickened that to the naked eye the cut surface presented what seemed to be a layer of pure greenish-yellow pus of half an inch thickness, separating the mucosa from the serosa. This thickness dwindled gradually as the œsophagus was approached, but even at this end the wall was noticeably swollen, and although not presenting so definite a collection of pus, yet exuded purulent fluid from the cut surface. An interesting feature was the sudden stoppage of purulent infiltration at the gastro-duodenal junction, the thickened pylorus changing suddenly to the thin and normal duodenum. There was no perforation of the wall and the serous surface was fairly normal. The duodenum was dilated, but together with the remainder of the alimentary canal appeared normal. There were a few reddish, soft glands in the neighbourhood of the stomach. Liver 56 oz., firm, brownish and mottled, with yellowish areas of varying size. Spleen 3½ oz., soft, friable, and dark purple. Pancreas normal. Kidneys 3½ oz. each, with adherent capsules, cortex diminished, consistence firm but flabby, section pale brick red. Bladder normal. Adrenals soft, friable, cavitated (p.-m. change), and yellow. Uterus and appendages senile. Lungs engorged and œdematous. Heart 8 oz.; muscle dark; some atheroma of one coronary artery, but arteries mostly normal.

Histological appearances of tissues fixed in Müller's fluid and cut in paraffin were as follows: At the œsophageal end the process was less advanced. There was diffuse cell-infiltration of all the coats but especially the submucosa, which was swollen and almost completely disorganised. The fibres of the muscular coat were split asunder by the infiltrating cells, which extended with diminishing severity to the serosa, beneath which the vessels (as elsewhere) were engorged with red corpuscles and many leucocytes and the lymphatics choked with round cells. The infiltration extended also through the muscularis mucosæ, which was little affected, to the basal portion of the mucosa, and to some extent between the glands themselves, the lymphatics here also being distended with cells. The epithelium was fairly normal. The vessels were markedly hyperæmic, with excess of

leucocytes, which further aggregated in their vicinity more closely than elsewhere.

At the pyloric end the submucosa was represented by a thick, dense layer of leucocytes, widely separating the muscularis mucosæ from the partly disorganised muscular coat. The engorged vessels were in places surrounded by fibrinous exudation. The outer portion of the muscular coat could still be distinguished, though numerous leucocytes were present amongst the fibres. The muscularis mucosæ and mucosa were similar to the pyloric end.

The swollen lymph-glands were engorged and inflamed. The liver was hyperæmic and in some of the portal canals there was marked engorgement, with some slight cell-infiltration and in places fibrinous exudation. The kidneys showed interstitial nephritis.

*Bacteriological examination.*—Films of the pus showed Gram-staining cocci arranged in short chains, some of the cocci staining more feebly than the rest. Similar organisms were found abundantly in sections of the stomach-wall, lying in and between the leucocytes infiltrating the submucosa, etc.

Peptone bouillon inoculated with a loopful of splenic pulp gave in twenty-four hours a pure culture of streptococci. Growth also occurred in agar, and subcultures were obtained on the same media. No animal inoculations were performed and the organism died out shortly.

Films from the tonsils showed so large a variety of organisms that no conclusions could be drawn.

The interesting features of this case are: (1) the primary affection of the stomach, to which part of the alimentary canal the lesion was solely confined; (2) the general diffuse purulent infiltration of the submucosa; (3) the finding of streptococcus.

There appears to be no doubt that the streptococcus was the causal agent, but as to the mode of infection there is some uncertainty.

There was nothing in the mucosa to suggest any local lesion as the site of infection. The tonsils were certainly a little enlarged with suppurative foci, but this is found so frequently in non-septic cases that little can be said of it beyond suggesting the possibility of such an infection.

It may be that the alcoholic bout superadded to the chronic

alcoholism had so lowered the resistance of the stomach by its local action as to permit of the organisms settling in the more delicate and vascular submucosa and there developing.

In other cryptogenic infections it seems as if the organism locates itself in tissues undergoing some unusual strain—*e. g.* in osteomyelitis and the septic nephritis of pregnancy.

The submucosa allows of easy spread of pus and great distension in virtue of its anatomical structure, the muscles on one side and the muscularis mucosæ on the other preventing escape of pus into the cavities.

Robson and Moynihan briefly summarise all the cases hitherto recorded—85 in number. Of these 63 appear to be of the diffuse variety and 11 definitely circumscribed abscesses, the remainder either recovering or not coming to autopsy and being diagnosed from the existence of severe gastralgia and vomiting of large quantities of pus.

The ages of the diffuse varieties varied from twenty to sixty, though the four youngest were ten, eleven, seventeen, and nineteen. In most the pus was not regularly distributed but accumulated in greater amount at the pyloric end, though in one case it was more marked at the cardiac end.

The etiology varied. A definite alcoholic history existed in eight, though the occupations of the remainder would suggest an increase of this number. Two were pyæmic and one was due to swallowing of pus from a suppurative stomatitis, the pus probably so affecting the stomach as to inhibit the normal destructive action of the gastric juice on organisms. The other causes included marasmus and bad diet, chills, trauma, and, in a few, ulcers simple and malignant.

In the later cases bacteriological examinations were made, and in seven streptococci were found and isolated in all but one, where the cultures were overrun by the *Bacillus coli*. In one, which followed chronic bronchitis and bronchiectasis, streptococci were isolated from the stomach and the lung-cavities.

Vomiting of pus, sometimes in large quantities, seems to be a constant symptom, but in this case the vomiting was certainly not marked after admission and no pus was noticed, and, indeed this could only occur after perforation of the mucosa.

REFERENCE.

*Robson and Moynihan.*—'Diseases of Stomach,' 2nd edition, 1904.

*February 20th*, 1906.

## 16. *A nose with supernumerary nostrils.*

By B. LINDSAY.

FOR a description of this curious case I am indebted to the courtesy of Dr. J. P. Elliot, of Bellingham, Northumberland, by whom the patient was sent up for operation, and of the operating surgeon, Mr. Rutherford Morison, and other officials of the Royal Infirmary, Newcastle-on-Tyne.

The congenital condition of the parts, destroyed by the operation, is recorded by photographs taken at the infirmary,

FIG. 34.

Showing the duplication of nostrils described; tracings made from photographs.

and from these the accompanying outlines have been traced. The nose, normal as regards the upper part, has two sets of separate nostrils, with one continuous median septum; and it is remarkable that these nostrils are arranged *in serial order*. Each nostril is symmetrical with its fellow on the opposite side of the median line of the nose; and the nostrils on the same side of the nose, with their adjacent parts, are serial repetitions of one another. Upper border, that is, corresponds with upper border and lower border with lower border, not adjacent border with adjacent border. The absence of the latter form of symmetry, a form characteristic of extra parts produced by dichotomy, is especially to be noted.

Both pairs of nostrils opened freely into the nasal cavity, so

that the patient breathed through all four. It is evident, however, from the appearance of the mouth in the photograph, that she did not breathe very comfortably. The septum of the nose was somewhat elongated, in correlation with the presence of the extra nostrils. There was a slight crookedness of the two sides of the nose, but not greater than is often the case in normal noses. There was no history of the occurrence of any other nasal deformity in the family. The upper pair of nostrils was removed by operation, the lower pair being retained.

*Discussion of the serial arrangement of the parts and of its possible interpretation.*

In view of the unusual character of this redundancy, a few remarks regarding its theoretical aspect may be of interest.

To interpret it as presenting a trace of lost metamerism in the facial region is a temptation obvious at first sight. The suggestion is perhaps worth criticism.

What traces of primitive metamerism are there to be found in the structure of the head and face? This question embodies one of the half-solved problems which the founders of comparative morphology have left as a legacy to the biologist of the twentieth century. Professor Marshall's theory of the cranial nerves remained incomplete at his death. Professor W. K. Parker laboured for years at a theory of pre-oral metamerism, which was eagerly expected by his contemporaries, but which never attained a definite form. Less cautious workers, in the early days of morphology, did not hesitate to refer the nose, and also the lens of the eye, to an origin in pre-oral members of the series of gill-clefts. To homologise the seats of the sense-organs in this way was a possibility almost irresistibly suggested to the theorist, at a date when the connection of the ear with a gill-cleft had been but recently explained. Modern morphology has, however, wholly rejected any such view regarding the origin of the nose. The main argument adduced against it consists in the entirely superficial character of the nostril in the lowest vertebrata, and in the comparatively late phylogenetic development of the nasal passages. But those who have laid most stress on this argument have perhaps hardly given a fair hearing to the case for the other side. They have ignored the

fact that a gill-cleft consists of two portions, an epiblastic and a hypoblastic part. If the latter has become obliterated, there is no reason why the former should not survive independently, and afterwards become connected up with the mouth or pharynx by new passages of later phylogenetic date.

It is obvious that the theorist who should venture to refer the development of the nose to the origin above indicated might go a step farther. The supernumerary nostrils seen in this case might then be explained as an extension of the series of clefts. For a series of structures that has undergone restriction in the course of phylogeny, sometimes, by a sport presumably atavistic, adds to its number; in this case the addition does not necessarily represent the exact form of any individual lost member of a series; it may merely express the general tendency of the series. From the point of view of the theory given above it will be observed that the redundancy shown in the case under consideration affects primarily the nostril, phylogenetically the oldest part; while the deeper structures of the nose, phylogenetically more recent, are not affected.

I have given above a fair statement of the case for a theory which is considered obsolete, but which is certainly of interest in the present connection. I am far from being prepared to commit myself to supporting any such theory, or to entering upon that discussion of the value of the nasal neuropore in the larva of *Amphioxus* which any such theory involves. On the contrary, I will make a present of the facts of this case to the advocates of the theory of the "parallel evolution" of metamerism, and of its "sporadic" appearance in animal groups which are not genetically connected. If anywhere in the whole wide world of comparative morphology the "sporadic" (!) occurrence of metamerism has an existence, other than in the internal consciousness of theorists, then it may reasonably be claimed that it is shown here.

### *Serial redundancies; a discussion of some examples.*

It is worth while to recall a few instances which present, so to speak, a revival of the numerical potentialities of a restricted series. The occasional tail of *homo* and the occasional supernumerary ribs are instances of this; here the actual form of

lost serial parts seems to be more or less accurately revived. A well-formed sixth digit on the outer side of the hand probably affords another instance, but with a certain difference. Here the extra finger expresses the potentialities of a digital series derived from a fin with an indefinite number of rays, and perhaps, intermediately, from a pre-reptilian paw with more than five digits—I believe the number seven has been suggested. Yet it is neither a fin-ray nor a claw; it expresses an ancient potentiality in terms of modern phylogeny, and takes on the approximate characters of its next neighbour in the row. This point is of interest in the present connection. (I have implied a criticism of Gegenbaur's dictum that remote atavism must not be assumed. It is a dictum that admittedly requires considerable modification. The phrase I have used here, "ancient potentiality expressed in terms of modern phylogeny," will be found to be curiously applicable in many well-known instances of atavism.)

Parallel cases of the extension of a restricted series are to be found among vegetable forms. The "whorl" of the various floral organs in a typical phanerogamic flower has been established by the restriction of an indefinite series, viz. of the continuous spiral order of the parts round their axial support. The uneven joining of the beginning and end of the "whorl," originally set at different levels, has tended to be obliterated, in the course of phylogeny, but survives, to the teratologist, in the curious straight lateral "seam" which we sometimes see in an orange or other fruit, marking the junction, the imperfect junction, in the whorl of carpels, of its beginning and its end. Supernumerary variations of these restricted series, the floral whorls, constantly occur—an extra petal, or sepal, or bract, an extra stamen, usually correlated with an extra member in the floral envelope, less frequently an extra carpel. Small indications are often present which serve to distinguish these serial supernumeraries from extra members produced by dichotomy.

A still more familiar instance of the same thing is the "four-leaved clover," with its associated variations of five, six, seven leaflets, or more. This exhibits a return to the leaf-type characteristic of its order, by the revival of lost leaflets or pairs of leaflets belonging to a pinnate series. The result is often a leaf frankly pinnate.

In both these instances we constantly get, side by side on the

same plant or on kindred plants, examples of the serial supernumerary and of the extra member produced by dichotomy; also there are "doubles" regarding which it is impossible to say whether they are the product of the fission of one or of the fusion of two.

It thus appears that the modes of variation which produce supernumerary petals or leaflets are point for point the same with those that produce supernumerary fingers; for in the case of the latter we find well-formed fingers that may be put down as instances of serial extension, as well as more frequent instances of imperfect fingers formed by dichotomy, and occasional instances that suggest fusion. Nothing, in fact, brings home to the biologist more forcibly than the study of teratology the oneness of animal and vegetable life. In both we meet with the same phenomena, with the same histories of suppression and of revival, of redundancy and of deficiency, of adhesion and of separation, of disproportion, of premature development, or of premature arrest.

*Other possible interpretations of the structure described in this case.*

Obvious at first sight as a temptation equally with the theory discussed, is another theory, which I name only to dismiss it. I refer to the possibility of the division of each nostril into two parts by an abnormal development of the nasal cartilages. In some animals (*e. g.* cat and dog) the division of the external nostril into an inner (median) part and an outer part, by an overhanging angle of cartilage, is very marked. There are not wanting types of human nose in which the superjacent cartilage encroaches (to a slight degree) on the curve of the upper border of the nostril. Given the presence of such an angularity, and its abnormal adhesion to the septal border of the nostril during embryonic life, and a double nostril might thus be produced. But a glance at the diagram is sufficient to negative this theory. No such bar of cartilage divides the two nostrils, each of which has its own proper boundaries, approximately normal in shape. The structure presented by the case was, in fact, aptly described by the operating surgeon as "one nose superposed on the top

of another," the continuous septum being common to both of them.

Hitherto we have left out of sight the possibility that the structure described is a "double," due to dichotomy. The main objection to such a view lies in that absence of symmetry in adjacent parts of the reduplication which has already been emphasised. If, however, the case is a double, the doubling has taken place symmetrically on both sides of the median plane, and across planes which meet the latter at corresponding angles.

There remains the possibility of a pseudo-dichotomy produced by some kind of injury at an early embryonic stage. The existence of any direct injury or perforation of the tissues is in the highest degree improbable. We owe to Dr. Mott a warning, which has become classical, against the mistake of ascribing the atrophy of parts to the action of abnormal conditions during embryonic development. The same principles are applicable in the question of injury or redundancy as in the question of atrophy or agenesis. A possible exception suggests itself, to which I shall presently refer.

### *General considerations regarding double growths in animal and vegetable organisms.*

Division by two is a fundamental law of growth in both animal and vegetable organisms. To discuss the meaning and the distribution of the incomplete division usually spoken of as dichotomy is beyond the scope of the present paper. The tendency to dichotomy decreases as we ascend in the scale of existence. The recrudescence of a tendency to dichotomise in the free extremities of growing parts is, therefore, in organisms of a high grade, probably to be ascribed to atavistic degeneracy. If so, it falls under the definition I have given above, of ancient potentiality expressed in terms of recent phylogeny. The tendency to division by two is as old as protoplasm; the part divided may be a structure of the most recent phylogenetic date.

In the case of plants a theory has been propounded that leaf-doubles are occasionally due to injury by insects. So far as I am aware, this theory has not received much attention; but after several years' study of the question I am inclined to think

that there is distinct evidence in its favour.[1] Such a possibility necessarily opens up the question of induced dichotomy in animal structures also. In view of the well-known experiments of Driesch on Echinoderm embryos, and of Wilson on the embryo of *Amphioxus*, we are obliged to admit that similar cells in an embryonic tissue sufficiently young may have similar and independent powers of development. Given an injury such as to divide a growing point into two masses of cells, we might therefore expect a dichotomised structure as a result. With the permission of Dr. Mott, I should like to suggest that pressure, causing arrest in the direct line of growth, might possibly lead to the separation of a growing tissue into two such masses. We have here a rival theory to that of dichotomy by atavism, and one which may possibly have a bearing on the present case.

## Appendix.

### *Copy of clinical record in the Infirmary Library, Newcastle-on-Tyne.*

*Double nose.*—Congenital deformity; age of patient, 14 years; occupation, school. Operation, plastic. Admitted with double nose, one superimposed on the other, the condition being shown in the accompanying photographs.

*Operation.*—Vertical incision down middle line of upper surface of nose, joining transverse incision across the septum between the two pairs of nostrils. Flaps (skin only) dissected back on either side. Upper pair of nasal cartilages removed completely. Lower nostrils packed with gauze. Flaps sutured with fine catgut and silkwormgut.

*Temperature.*—Recorded for two days: rise from 98° to 98·4° F. in evenings.

### *Copy of part of Dr. Elliot's letter, with report of the case up to February 14th, 1906.*

(1) I find that the upper and under nostril on each side open directly into the nasal cavity, and that they do not continue as separate passages.

[1] Shattock has several times produced dichotomy of the root in *Faba vulgaris* by hemisection of the growing point. The faces of the two resulting roots, however, are histologically imperfect, being devoid of root-hairs ('Path. Soc. Trans.,' vol. xlviii, p. 261).

(2) The parts are not quite symmetrical on either side. There is an indication left of the right nostril, viz. the upper one. They —*i. e.* the nostrils—are often suppurating on either side.

(3) She breathes perfectly, but makes a horrible noise whilst sleeping.

(4) Before the operation she breathed through all her nostrils.

(5) There is no family history of any defect or deformity on either side of the family.

*May 29th*, 1906.

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## 17. *Diphtheria of the œsophagus.*

By JOHN FAWCETT.

A. C—, a female patient, aged 35 years, was admitted into Guy's Hospital, under the care of Mr. Lane, on February 10th, 1906. She had had double öophorectomy performed about thirteen years previously, and in 1901 the appendix cæci was removed. Laparotomy was performed on February 12th, 1906, and a number of peritoneal adhesions were separated. On March 23rd a second operation was carried out, after which the patient suffered severely from vomiting for seven or eight days, but then improved and appeared for a time to be progressing satisfactorily.

April 6th.—Patient developed a cough, and complained of a soreness of the throat.

April 8th.—A branched cast of the trachea and main bronchi, 3¼ inches long, was coughed up. Patient was very hoarse, and attempts to swallow gave her much pain. Temperature, 101·4° F.; pulse, 140; respiration, 32.

April 9th.—The temperature steadily rose, reaching 103·4° F. at 6 p.m. For the last few days there had been increasing signs of bronchitis with much cyanosis. The patient died the following day.

The temperature was normal or subnormal until April 1st; after that date it varied between 98° and 100° F., and on the evening of April 7th it rose to 100·8° F.

The patient was in a somewhat precarious condition for some time after the second operation on March 23rd, but previously to the onset of the sore throat on April 6th there was no evidence of any complication, and she appeared to be progressing favourably, although the temperature had been slightly above

normal since April 1st, and the pulse rate had remained rapid, viz. from 112 to 120 a minute.

*Autopsy.*—The œsophagus was lined throughout by a thick layer of wash-leather-coloured membrane; over the lower 9 cm. the membrane was not quite so thick as above, patches of inflamed and congested mucous membrane showing through it in places. The stomach was not involved, the membrane being limited by the lower margin of the gullet. The right tonsil had a patch of membrane on its surface, and the epiglottis, larynx, trachea, and bronchi, even to their smaller ramifications, were covered with membrane which formed a complete mould of these tubes and was of much firmer consistence than is usual. There was some recent pleurisy on the left side and a diffuse bronchopneumonia in the lower lobes of both lungs.

On microscopical examination the diphtheritic membrane in the œsophagus was found to be composed of a fibrillar hyaline matrix, in the interstices of which were groups of closely packed leucocytes, and some large flattened cells, probably degenerated squamous epithelial cells. The epithelial lining had been completely destroyed in the portion which was examined. In the submucous coat there was considerable small-celled infiltration; the outer layers of the gullet were normal in appearance. Klebs-Loeffler bacilli were found in cultivations made from the œsophagus, the larynx, and from the heart-blood.

*Remarks.*—Diphtheria involving the œsophagus is very rare, and in most cases is a part of a widespread infection and secondary to diphtheria affecting some part of the respiratory tract. I have only been able to find records of two recent cases, viz.:

(1) A boy, aged 8 days, in whom the membrane extended down the œsophagus to within an inch or so of the cardiac orifice of the stomach (see 'Trans. Path. Soc.,' vol. xlvii, p. 39, Dr. E. W. Goodall).

(2) A boy, aged 18 months, whose œsophagus exhibited membrane in its upper third, and in whom the pyloric region of the stomach was also involved (see 'Reports of the Society for the Study of Disease in Children,' 1902–1903, vol. iii, pp. 234–239, Dr. E. Cautley).

Welch and Schamberg, in their book on 'Acute Contagious Diseases,' have no special reference to this class of case, except that they refer to a report by Councilman, Mallory, and Pearce,

who found membrane present at autopsy in 127 out of 220 fatal cases of diphtheria, and in 12 of these there was membrane in the œsophagus.

Sir Morell Mackenzie, in his book on 'Diseases of the Throat and Nose,' refers to ten writers who have published cases. From amongst these Mackenzie mentions Steffen as having recorded fifteen cases, nearly all of which were complicated with one or more of the following conditions, and so may not have been true diphtheria, viz.: with pneumonia, tubercle, chronic peritonitis, intestinal catarrh, follicular enteritis, caseous bronchial glands, and abscess in the spleen.

Mackenzie mentions two cases which had come under his own observation, one in a child aged 3 years and another in a boy aged 6 years, in both of whom portions of the respiratory tract were also involved.

The case which is here recorded is of interest in that it occurred in an adult; although the affection is of so marked a type, yet it gave rise to little or nothing in the way of laryngeal symptoms, and no suspicion of diphtheria was raised during life, even when a cast of the bronchi was coughed up.

The membrane in the œsophagus was strictly limited to this tube, and so probably was the result of a direct infection from the pharynx, and therefore different in its mode of origin to the cases described in the 'Trans. Path. Soc.' by Dr. Soltau Fenwick and Dr. F. Willett, in which the stomach was affected and the œsophagus was free from membrane.

*May 15th*, 1906.

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18. *Symmetrical adenomata or nodular hyperplasia of the suprarenal glands, and extreme sclerosis of the aorta and coronary arteries.*

By F. Parkes Weber.

In 1903 O. Josué (1) succeeded in experimentally producing calcareous deposits and lesions resembling atheroma—that is to say, what the Germans generally term "arteriosclerosis"—in the aorta of rabbits by repeated intravenous injections of small doses of adrenalin.[1] His experiments have since then been

[1] In rabbits weighing over 2 kilogrammes Josué injected three drops of a 1 per mille solution of adrenalin every two days into the veins of the ear. Loeb and Githens (15) found that injections given at intervals of four days had more effect than the same number of injections of the same quantity given close together.

repeated and in great part, or entirely, confirmed by a number of separate observers (References, 3–15). The facility with which this "experimental atheroma" can be produced differs in different individuals. In some rabbits aortic lesions may be found after only two or three adrenalin injections.[1] The lesions, which may progress to actual aneurysmal formation, can be easily produced by intravenous injections, or, according to Külbs (12), by intra-tracheal injections, in old rabbits, but not in very young rabbits (Pic and Bonnamour, 5), nor in dogs (4), nor by subcutaneous injections, even in rabbits (Külbs, 12). According to Loeb and Githens (15) it seems probable that pregnant animals are less susceptible to the harmful action of adrenalin than are others. These observers found that adrenalin injections do not interfere with the course of pregnancy or delivery in rabbits, and have no effect on the development of the vascular system of the fœtus. The same observers found that renal lesions (produced by the administration of potassium chromate or by ligature of one ureter) and the consequent interference with the elimination of adrenalin did not appear to increase the susceptibility of rabbits to the vascular changes induced by adrenalin. According to the experiments of L. Lortat-Jacob and G. Sabaréanu (19) it appears that removal of the thyroid gland renders rabbits less susceptible and removal of the testicles makes them more susceptible to these harmful effects of adrenalin injections. Loeb and Githens (15), however, found that adrenalin atheroma occurred in spite of thyroidectomy. Diet seems to make some difference. According to A. von Koranyi (21) rabbits fed on turnips, etc., are less easily affected by experimental (adrenalin) atheroma than those fed on oats, and iodine in the form of subcutaneous injections of iodipin appeared to hinder the arterial changes in the animals experimented on (see also P. Boveri, 21).

I cannot here enter into the part played by excessive arterial blood-pressure in the production of "experimental atheroma." Lissauer (9) points out that the aortic lesions appear too early (in a few weeks)[2] to be explained on any mere blood-pressure

[1] The vascular lesions generally appear in a few weeks by Josué's method. In some animals the changes occur after only two to eight injections (1, 3, 11, 15). Braun (11) even says that experimental atheroma lesions may commence after only one or two injections.

[2] According to Josué (1), Rzentkowski (3), Braun (11), and Loeb and Githens (15), the aortic lesions may appear in some rabbits after only one or two (Braun) to eight adrenalin injections.

hypothesis. Loeb and Githens (15) found that intravenous injections of pyrocatechin, which have been shown by Dakin (16) to cause marked rise in blood-pressure, were quite incapable of producing any vascular lesions in rabbits comparable to those produced by adrenalin. Sturli (10) from his experiments with methylamin-acetopyrocatechin and adrenalin, and Mironescu (22) from his trials with euphthalmin and adrenalin, conclude that experimental atheroma in rabbits is due to a direct toxic action of the adrenalin on the arterial wall, though the latter observer admits that changes in blood-pressure, due to the adrenalin, may favour the production of the arterial lesions in question. Josué (quoted by Loeb and Githens, 15) found that nicotin, though it causes a rise of blood-pressure, has no effect on the structure of the vessel walls. L. Braun (11) found that the simultaneous injection of amyl nitrite, though it prevented rise of blood-pressure, did not prevent the occurrence of the adrenalin lesions, but von Koranyi and also P. Boveri (21), as already stated, found that iodine hindered their appearance.[1]

It is interesting to note that, as R. M. Pearce (14) and B. Fischer (4) have shown, Josué's method of adrenalin injections produces myocardial in addition to arterial disease, and that the myocardial changes thus produced are by no means all secondary to stenosis of the coronary arteries. In about half the number of animals experimented on in which the heart changes were examined severe myocardial lesions were found unaccompanied by arterial disease (Pearce, 14). The pulmonary artery seems never to be affected (4 and 12).

Many of the observers have denied the identity of Josué's "experimental atheroma" with the atheroma of the aorta and large arteries which is frequently found at *post-mortem* examinations on human beings. W. Erb, junior (16) and some others (7, 8, 9, 14) of those who have repeated Josué's experiments, believe that artificial atheroma produced by adrenalin injections in animals is not analogous to human arterial atheroma, but regard it as more nearly resembling the primary calcification of

[1] For a discussion and summary on the physiological action of adrenalin on unstriped muscular tissue see T. R. Elliott, "The Action of Adrenalin," 'Journal of Physiology,' Cambridge, 1905, vol. xxxii, pp. 401 to 467. In regard to the connection between experimental atheroma and changes in blood-pressure see also H. Batty Shaw, 'Lancet,' 1906, vol. i, p. 1459.

the middle coat, which has been especially investigated by J. G. Mönckeberg (25), sometimes met with in the arteries of the arms and legs in man. The syphilitic aortitis which leads to the development of aneurysms in man is now believed by many to be a proliferative or plastic mesaortitis, the "mesaortitis productiva" of H. Chiari (24). According to Albrecht (17) the adrenalin lesions by their localisation and their tendency to lead to aneurysmal dilatations resemble the results of this syphilitic aortitis, but differ from them by the presence of primary necrotic changes in the media and by the ready disappearance of evidence of any original inflammation. On the other hand, as the suprarenal capsules appear to be especially invaded by the *Spirochæta pallida* in congenital syphilis, it has been suggested (Josué, 18) that changes originally set up by the spirochætæ in these glands may constitute a connecting link serving to explain the frequency of ordinary aortic atheroma in syphilitics.[1]

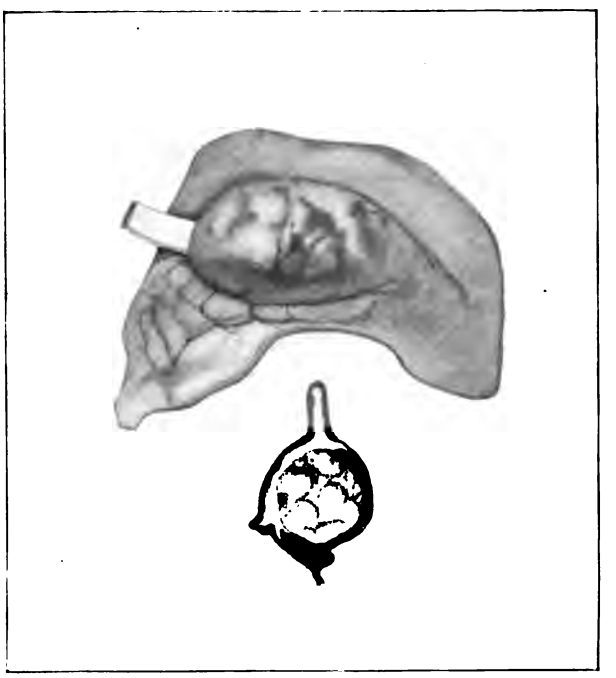
Josué (2), and Widal and Boidin (23), have drawn attention to the association of generalised atheroma with hypertrophy and adenomata of the suprarenal capsules, and it is to a case of this nature to which I now wish to draw attention.

The patient, a German, Michael F—, aged 59 years, weighing 76 kilogrammes, was admitted to the German Hospital on March 15th, 1906. Very little past history was obtained. For several months he had been suffering from shortness of breath and cough, with slight expectoration. For some weeks his legs had been swollen. Examination of the thorax showed the presence of pulmonary emphysema. Dry sounds were heard all over the lungs, and there were occasional crepitations over the lower lobes. The heart was evidently abnormally covered by lung-tissue; the apex beat could not be felt, and the sounds were faint; no murmur could be detected. Pulse 88, regular; the radial artery felt rather too hard; the brachial blood-pressure as measured by the Riva-Rocci apparatus with the broad band, was 130 mm. mercury. The liver could be felt about three fingers' breadths below the costal margin. The spleen seemed not to be enlarged.

[1] Similarly in regard to the connection between chronic saturnism and arterial disease, it may be noted that Gouget (14) has experimentally produced hypertrophy of the suprarenal capsules as well as aortic atheroma in a guinea-pig by the administration of carbonate of lead.

There was a scar in the abdomen from an old laparotomy wound (an operation had been performed six years previously) with a ventral hernia in the scar. Both legs were œdematous and the arms slightly so. The urine was of specific gravity 1·025, free from sugar, but containing a little albumen (under ½ per mille by Esbach's tube); a few hyaline casts were seen

FIG. 35.



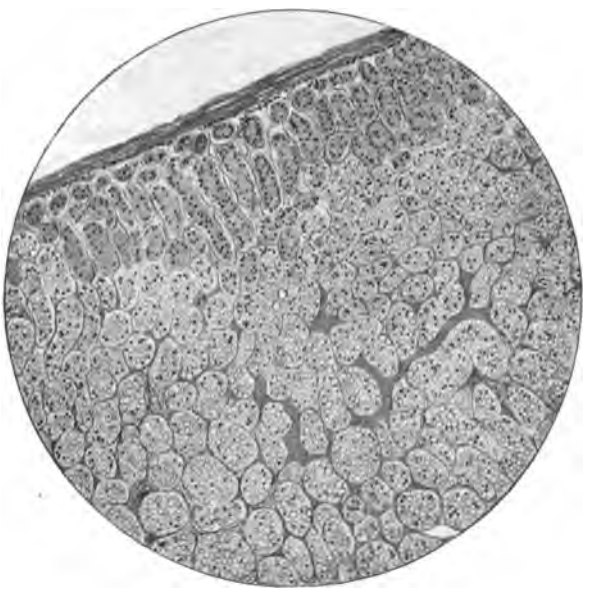
Showing one of the adrenals with the adenoma projecting from the surface, and a vertical section of the same. In the latter the cortical substance is represented darker than the medullary.

in the sediment obtained by the centrifugal machine. There was no fever. The patient died suddenly three days after admission.

At the necropsy (on the following day) the *heart* showed moderate hypertrophy and much dilatation, chiefly of the left ventricle. Both coronary arteries were greatly sclerosed; at parts they were quite rigid and their lumens greatly narrowed, if not completely blocked. Portions of the myocardium, notably

portions close to the internal ventricular surface, had obviously undergone degenerative changes, probably secondary to the coronary artery disease. There was some *ante-mortem* thrombus at the apex of one of the ventricles. The aorta (especially the abdominal portion) showed extreme sclerotic changes with deposition of calcareous plates. In our examination of the abdomen no explanation of the old laparotomy was forthcoming. The liver, somewhat enlarged, was "nutmeggy" from chronic passive

FIG. 36.



A microscopic section showing part of the tumour of the cortex and the large vacuolated fatty cells of which it mainly consists. (Zeiss A.)

congestion. The kidneys were of good size, but there was naked-eye evidence of a certain amount of chronic interstitial nephritis. The spleen, slightly too large, contained an old infarct.

The suprarenal glands together weighed about 19 grammes. Imbedded in the cortical substance and projecting on the surface of each gland there was an oval-shaped nodule, measuring about 25 × 15 × 15 mm.—that is, about as large as an ordinary Muscat grape. A microscopic section (from the right capsule) shows one of these nodules to have the typical structure of an ordinary suprarenal adenoma—*i. e.* of a hypertrophic

nodule of the cortical substance, with the customary fatty degeneration of the cells. A section of one of the nodules especially stained with Sudan III (for which I am indebted to the kindness of Mr. Shattock) shows that the cells are loaded with fat-globules. The suprarenal medullary substance seems not to be affected except by pressure due to the cortical growth. One of the suprarenal capsules and part of the atheromatous aorta from the case are preserved in the Museum of the Royal College of Surgeons.

By microscopical examination it was found that the degenerative and calcareous change in the aorta was by no means confined to the inner coat, for the middle (muscular) coat was extensively involved. Even in relatively little affected spots of the wall of the aorta the unstriped muscle of the media appeared hazy and degenerating, and showed a deposit of very fine granules (the earliest stage of calcification). Both in the middle coat and the outer coat (tunica adventitia) there were likewise scattered spots of small cell infiltration. The question arises whether the aortic disease in the present case may not be regarded as specially resembling Chiari's "mesaortitis productiva," and the "experimental" mesaortitis (or rather "mesarterionecrosis" of the aorta) produced in rabbits by intravenous adrenalin injections.

I take this opportunity of thanking Dr. Schuh, house physician at the German Hospital, for preparing sections of the aorta and suprarenal capsule.

The present case is of some interest as it fits in with Josué's views (2) of a causal connection between suprarenal adenomata (or hyperplasia of the cortical gland substance) on the one hand and aortic and generalised atheroma on the other. Of course, the association may be a chance one, but it must be remembered that neither the symmetrical adenomata of the suprarenal glands nor (even in old persons) the extreme changes in the aorta and coronary arteries are common conditions.

Whereas in adults there is perhaps some causal connection between atheroma-like aortic lesions and suprarenal hypertrophy, there seems in children to be certainly a causal connection between the presence of suprarenal hypertrophy or hypernephromata (that is to say, tumours derived from the suprarenal cortical gland-cells) on the one hand and precocious general and

sexual development on the other. An excellent summary on the relation of the suprarenal glands to the sexual organs has been recently given by W. Bulloch and J. H. Sequeira at the Pathological Society of London (26). It is possible, then, that overgrowth of the suprarenal glandular tissue (and excess of the suprarenal secretion) may be connected with different general conditions according to age—*i. e.* in childhood, with precocious development and after middle life with arterial atheroma. One might point out a possible analogy in the case of the hypophysis cerebri. Overgrowth of pituitary gland during the growing period of life may be connected with gigantism, and after the normal period of growth has ceased with acromegaly.

In regard to the action of adrenalin injections in animals it may be remembered that Pic and Bonnamour (5) failed to produce "experimental atheroma" by Josué's method in rabbits that were still very young. It would therefore be very interesting to know whether in young (still growing) rabbits or other animals repeated but relatively very minute injections of adrenalin could produce precocious general and sexual development in place of the aortic changes it produces in old rabbits.

## Addendum.

Since writing the above account I have had the advantage of hearing some friendly criticism on it. Mr. S. G. Shattock in particular points out that "adrenalin" is furnished from the medulla, but not from the cortical substance of the suprarenal glands, and that in the present case, as far as the microscopic examination went, no decided changes were found in the medullary substance, the adenomata being undoubtedly of cortical origin; it has occurred to me, however, that the presence of suprarenal adenomata may possibly act as a mechanical irritant, both producing hyperæmia of the whole organ and stimulating the functional activity of the medullary cells.

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*May 29th*, 1906.

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## 19. *A case of tuberculosis of the tonsils and lymphatic glands, together with congenital bronchiectasis of both lungs and cirrhosis of the liver and pancreas.*

By J. Graham Forbes.

The case which I bring before the Society to-night is one of particular interest and rarity on account of the peculiar features

it presents in the association of tuberculosis of the tonsils and lymphatic glands, together with congenital bronchiectasis of both lungs, cirrhosis of the liver and pancreas.

Ethel C—, aged 2½ years, was admitted on January 21st, 1904, to the Hospital for Sick Children, Great Ormond Street, suffering from enlargement of the glands in the neck and swelling of the abdomen. She was under the care of Dr. Penrose, to whom I am indebted for the opportunity of publishing the case.

*History* (obtained from the mother) pointed to only ten days' noticeable illness, during which tender lumps appeared in the neck, increasing in size, and the abdomen became swollen. She also vomited, screamed much at night. The bowels were constipated. No history of cough, night-sweating, or wasting.

*Previous history.*—Full-term child. Breast-fed for fourteen months. Was treated in the Out-Patient Department at the Hospital for Sick Children for rickets and eczema in 1903.

*Family history.*—Parents healthy. Patient the youngest of three, others alive and healthy. Mother had had no miscarriages; no evidence of syphilitic taint.

*Condition on admission.*—Not wasted, but very pale; mucous membranes anæmic. There were enlarged veins on the forehead and upper part of the chest. Frontal eminences prominent; anterior fontanelle open. Ribs slightly beaded, and epiphyses somewhat enlarged. *Tongue* covered with a dirty fur. *Teeth* fair. *Tonsils* enlarged, ragged, and discharging. The glands on both sides of the neck were enlarged, soft, elastic, and matted together. No evidence of suppuration or inflammatory reddening of the skin. This glandular enlargement apparently extended down into the anterior mediastinum, for there was marked dulness to percussion over the manubrium sterni. There was also enlargement of the post-auricular, axillary, and inguinal glands particularly. *Chest*: heart natural. *Lungs*: slight impairment below the left clavicle. Breath-sounds weak both back and front. No adventitious sounds. *Abdomen* full, umbilicus pouting, no enlarged veins. Greatest girth = 19½ inches. Marked resistance over the upper half due to enlargement of the liver, which reached to the umbilicus and five to six fingers' breadth below the costal margin; edge sharp, surface smooth and not tender. *Spleen* could be felt extending two fingers' breadth beyond the left costal margin. No evidence of free

fluid. There was diarrhœa and vomiting on admission, and this continued irregularly.

On February 2nd the tonsils were excised. On microscopical examination well-marked tubercles and giant cells were found, with much cell-infiltration and areas of necrosis.

*Blood examination.* — Hæmoglobin = 60 per cent.; colour index = ·8 per cent.; red corpuscles = 3,776,000 per c.mm.; leucocytes = 30,000 per c.mm.

*Differential count* showed marked polymorphonuclear leucocytosis. Polymorphonuclears = 92·6 per cent.; large mononuclears = 3·6 per cent.; small lymphocytes = 2·8 per cent.; eosinophiles = 1 per cent. Red corpuscles showed nothing abnormal.

The further course of the case showed a temperature ranging between normal and 100° F., with nocturnal rises, occasionally sustained between 100° and 101° F. The glands in the neck and elsewhere became reduced in size. The enlargement of the liver and spleen persisted. Nothing abnormal was to be noted on examination of the lungs.

A second blood-count on *March 4th* showed a further diminution in the amount of hæmoglobin and in the number of red corpuscles. There was still marked polymorphonuclear leucocytosis. Hæmoglobin = 42 per cent.; colour index, ·55; red corpuscles = 3·638,000 per c.mm.; leucocytes = 29,500 per c.mm.

Differential count.—Polymorphonuclears = 91 per cent; large mononuclears = 2 per cent.; small lymphocytes = 7 per cent.; eosinophiles, none seen.

No other change was noted beyond marked wasting, and death occurred on March 14th.

*Post-mortem examination* made by the Medical Registrar, Dr. Baumann.

*Cranium.*—Brain and meninges natural.

*Neck and thorax.*—There were many glands of about the size of a hazel-nut in the anterior and posterior triangles of the neck, extending down into the mediastinum and along the course of the œsophagus into the abdomen. The glands were discrete, hard, and white on section.

The bronchial glands were much enlarged and on section showed caseous and calcareous areas.

*Lungs.*—Both small and collapsed, especially the right. On

the surface were large grape-like bullæ, particularly in the upper lobe, and the right lung was more affected than the left. On section they presented an extraordinary honeycomb appearance, practically the whole of the lung-tissue being replaced by numerous cysts of various sizes, separated here and there by patches and strands of white fibrous tissue. Such of the smaller bronchi which could be recognised were somewhat dilated.

FIG. 37.

A section of the right lung, showing the cyst-like bronchiectatic condition described in the text. ⅔ natural size.

*Heart and pericardium.*—Natural.

*Abdomen.*—Liver: Much enlarged, weighing 34½ oz., when fresh of a pale greenish colour; surface slightly roughened; substance hard and tough on section; marked thickening of capsule. The whole organ showed dense infiltration, with white, fibrous strands extending between islands of connective tissue, which in places were bile-stained and of greenish colour.

*Spleen.*—Enlarged and soft—lymphoid areas well marked.

*Stomach and intestines* appeared natural and showed no apparent changes in their lymphoid tissue.

*Mesenteric glands* were enlarged and firm, not matted together; on section they showed a few points of caseation.

*Pancreas* was enlarged and firm. On section the gland was seen to be traversed by fibrous strands radiating from small areas of white connective tissue.

All the organs affected were subjected to microscopical examination.

The cervical and mediastinal glands were tuberculous, showing

FIG. 38.

A microscopic section of the bronchiectatic lung. × 40.

well-marked giant cells and small caseating foci. In addition to the tubercles, the lymph-follicles and medulla contained abundant germinal and endothelial cells and eosinophiles. The mesenteric gland examined showed no caseating tubercles, but many giant cells of various forms, mono- and multinuclear. The follicles and medulla were scattered, with many large germinal and transitional cells. Some were phagocytic and contained included cells with vacuoles and granular protoplasm.

The lung showed scattered areas of consolidation, the alveoli being crowded with inflammatory and endothelial cells.

Elsewhere were seen many distended alveoli and bronchioles, some of which contained free cells and cast-off epithelium. There were also portions in which the alveoli were normal in appearance.

The walls of the bronchioles were much thinned, denuded of epithelium, but in places showed thickening, due to cell-infiltration.

The liver was the seat of a coarse, multilobular and a fine intercellular cirrhosis, traversed by fibrous strands, which linked together patches of young fibrous tissue and cell-infiltration,

FIG. 39.

Showing extreme cirrhosis of the liver in the same case. × 80.

including islets of compressed liver-cells, and cells arranged in column resembling flattened and proliferated bile-canaliculi. The areas of young connective tissue were composed of round, oval, and spindle cells, together with collections of inflammatory cells.

Most of the gland cells, where they were not compressed and atrophied by the overgrowth of the fibrous tissue, showed marked fatty changes, but large areas of the liver-tissue appeared healthy.

The pancreas showed very similar cirrhotic changes to the liver.

No trace of tubercle could be found either in lungs, liver, or pancreas.

The kidney showed congestion of the cortex and cloudy swelling of the cells of the convoluted tubules.

The spleen was congested. The Malpighian bodies showed hyperplasia of lymphoid cells and central necrosis.

No tubercles were to be found elsewhere than in the glands.

Section of rib showed an irregular line of ossification at the junction with the cartilage and other rachitic changes. Its

FIG. 40.

Showing the cirrhosis of the pancreas in the same case. × 80.

marrow was much congested, and contained many lymphocytes, and a few large mono- and multi-nuclear cells.

I am indebted to Dr. Still for the suggestion that the association of congenital bronchiectasis of the lungs with cirrhosis of the liver and pancreas in this case is probably no chance one, and that the lesions in the three organs may be due to one and the same cause—namely intra-uterine disease. As I have already mentioned, no history or direct evidence of the influence of syphilis could be obtained.

Towards the end of this paper I shall allude to the possible

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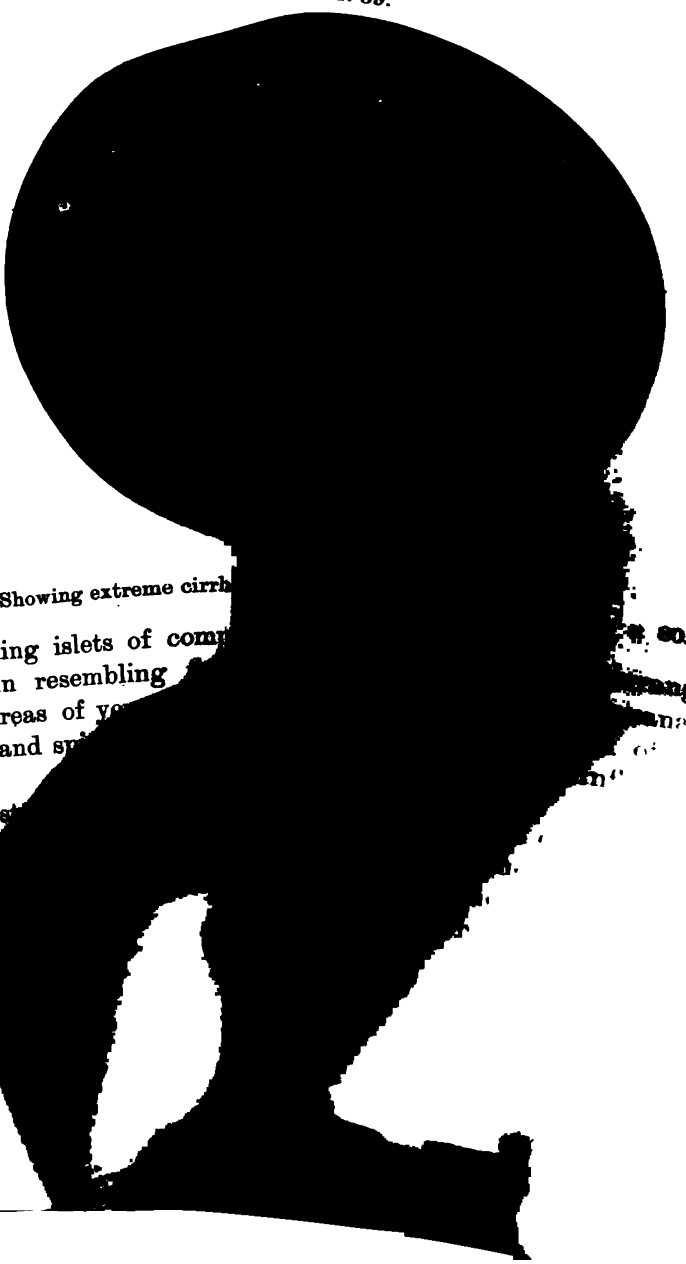
FIG. 39.



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firm, much fibrous tissue, mono- and multi-lobular cirrhosis, perihepatitis. Spleen enlarged. Mesenteric glands, caseous Tuberculous peritonitis.

In 13 of the 40 cases of cirrhosis there was a history pointing to the influence of syphilitic taint, and in 2 a probability of alcohol as the cause. In the 19 remaining cases no definite cause could be assigned. Four of them were cases of congenital absence or stenosis of the bile-ducts and gall-bladder, 2 were so-called cases of congenital icterus with biliary cirrhosis, in 1 there was also empyema, and in 1 pneumonia which may have played a part.

There remain 11 cases, therefore, in which the cause of the cirrhosis is a matter of pure conjecture; possibly they are congenital and date their origin from some developmental error during fœtal life, such as an overgrowth of the fibrous elements of the mesoblast already referred to.

How far tubercle may be assigned as one of the causes of cirrhosis of the liver in children is difficult to say. Considering the enormous number of tuberculous cases in which there is no trace of hepatic fibrosis, and the fact that I find only 6 cases in which the two are associated, leads me to suppose that the connection between the two is more curious than real.

At the same time, it has to be remembered that in 5 out of 40 cases of cirrhosis tuberculosis was present in one or other part of the body.

It is conceivable that under certain conditions of hygiene, bad feeding, and environment the tubercle bacillus or its toxins may play a part in producing cirrhosis of the liver, in the same way that malaria and congenital syphilis exert their influence.

A reference at this point must be made to the work of Hanot and Gilbert, who trace a close connection between tubercle and cirrhosis of the liver. They state that the tuberculous origin of some cases of cirrhosis has been definitely established, not only by the co-existence of tuberculous and cirrhotic lesions in the same liver, but also by etiological inquiry, which has positively excluded the influence of syphilis, alcohol, and malaria.

Three types of tuberculous cirrhosis are described:

(1) *Acute.*—Great hypertrophy of the liver, due to fatty changes and increase in the connective tissue, diffuse round-celled infiltration, with young fibrous tissue and giant cells.

(2) *Subacute.*—Resulting in a fatty and atrophic liver, with much fibrous tissue and giant-cell formation, macroscopically resembling the alcoholic form of cirrhosis.

(3) *Chronic.* — Hobnailed type of cirrhosis, with marked scarring and atrophy, resembling syphilitic liver.

Hanot and Gilbert also bring experimental evidence to support tubercle as a causal factor, and claim that they have produced cirrhosis of the liver in guinea-pigs as the result of inoculation with human tubercle.

They trace microscopical resemblances between the experimental form of cirrhosis in guinea-pigs and the acquired form in man, and consider that the development of tuberculous cirrhosis may be due to an individual resistance against the tubercle bacillus, or the natural attempt at repair in opposition to an infection by the bacillus in an attenuated form.

As is well known, cirrhosis of the pancreas is an exceedingly rare disease in children. I can find no other record of this condition among the *post-mortem* reports of the Hospital for Sick Children in the last forty-five years.

In Clifford Allbutt's 'System of Medicine' it is referred to as usually the result of congenital syphilis, but in the case I am recording there was no history or evidence pointing to inherited taint.

I now pass to the other peculiar feature of the case, namely the presence of congenital bronchiectasis of both lungs.

Among the *post-mortem* records of the Hospital for Sick Children, I have found altogether a total of 33 cases of bronchiectasis and bronchiolectasis; they include 30 cases of acquired and 3 (together with the present one) of congenital bronchiectasis.

In 11 of the 30 cases tubercle was present in the lungs, bronchial, and tracheal glands. In the remaining 19 cases either pleuritic adhesions, empyema, emphysema broncho-pneumonia, collapse, or fibrosis of the lung were also present. In 6 out of the total 33 a honeycomb condition of one or both lungs was present.

From the following description of 5 cases, in addition to the one recorded in this paper, I gather that 2 are due to congenital bronchiectasis.

Case 1.—Child, aged 7 weeks.

*History.*—Born with a papular eruption which has since

increased. Mother had three miscarriages before the birth of the patient.

*On admission.*—Puny child, covered with generalised papular and pustular eruption. The pustules were capped with yellow crusts which left shallow ulcers when detached. Sores on the lips, no snuffles, no soreness about the anus. Thorax: Heart natural. Lungs: Dulness to percussion and crepitations over both bases. Abdomen: *Nil.*

Two days after admission sudden dyspnœa and death.

*Post mortem.*—Thymus: Soft and large, weight 1 oz. 7 dw. 10 gr. Lungs: Presented a very striking appearance. On their outer surfaces and along their internal edges were many pearl-like bullæ, and at the bases large, dark-coloured areas of collapse. On section they both showed well-marked honeycomb condition, practically the whole of the normal lung-tissue being replaced by spaces varying in size from a hazel-nut to a large pin's head. No tubercles could be recognised. A subclavicular gland showed a few tuberculous points.

CASE 2.—T. H—, aged 1 year and 7 months.

History of cough for four or five months. No evidence or history of congenital syphilis.

*Post mortem.*—Lungs were scattered all over, with great air-bubbles immediately beneath the much thinned pleura. On section they showed numerous air-spaces, so that the whole lung resembled the structure of a sponge. The bronchial tubes contained only a little mucus. Right lung, weight 5 oz. Left lung, weight 4½ oz. No trace of tubercle. Liver and kidney showed marked fibrotic changes, and there was hypertrophy of the right heart. Possibly the changes in the lungs, liver, and kidney were due to the influence of some form of intra-uterine disease.

CASE 3.—G. S—, aged 1 year and 5 months.

*Lungs.*—Right: Emphysema and broncho-pneumonia. Left: Upper lobe was emphysematous. The lower lobe was made up of thin-walled cavities the size of a pea, separated by strands of fibrous connective tissue. No normal lung-tissue left. Condition described as bronchiectasis following atelectasis. No trace of tubercle.

The other two cases showed the condition of honeycomb lung, together with tubercle.

Case 4.—A. H—, aged 9 months.

*Lungs.*—Right upper lobe showed a caseous pneumonia, apparently secondary to perforation of the right bronchus by caseous mediastinal glands. Left upper lobe showed a honeycomb appearance like worm-eaten wood, holes being due to emphysema throughout the substance of the lobe. On the surface were several emphysematous bullæ. Left lower lobe showed a few tubercles.

Case 5.—C. H—, aged 7 months.

*Lungs.*—Right upper lobe adherent and studded with grey tubercles. Firm in texture and scattered with small caseous foci, elsewhere excavated by air-cavities giving the appearance of honeycomb. There was perforation of the right bronchus by the caseating bifurcation gland; other tracheal glands on the right side tuberculous. Left lung free from tubercle. Glands on the left side showed a few grey tubercles.

Congenital bronchiectasis of the lungs has been described as the result of malformation, intra-uterine disease, and, as is to be expected, syphilis.

Ewart quotes in Clifford Allbutt's 'System of Medicine' four different conditions:

(1) A form affecting usually only one lung, which may present a large central cyst branching into secondary and tertiary cysts (Meyer and Troenkel).

(2) Separate cysts formed on the smaller bronchi, some communicating with the bronchial lumen, others quite closed (Grawitz).

(3) Atelectatic bronchiectasis. Showing abnormal growth of the bronchial cartilages, with remnants of unexpanded fœtal lung-tissue (Heller).

(4) Due to obstruction of a bronchus by dermoid growth (Ogle, 'Path. Soc. Trans.,' 1897).

Malformation due to arrested development of the lung-tissue provides a possible explanation of this very interesting condition. The lungs are formed as a diverticulum of the ventral side of the gut at the junction of the pharynx with the œsophagus, and,

therefore, close to the fourth visceral arch. The tube, which is at first single, grows downwards into a mass of mesoblast in front of the gut, and soon gives off two pouches, of which the right becomes subdivided into three secondary pouches, while the left subdivides into two. The two primary pouches or bronchi send off secondary diverticula, the smaller bronchi and bronchioles, which ramify extensively and give rise to the infundibula and terminal alveoli. It seems possible to account for the congenital form of bronchiectasis by supposing that there has been an arrest of development at the infundibular or bronchiole stage previous to subdivision into the terminal alveoli. The state of lung would then resemble the normal condition found in the lower vertebrates, such as the frog, where the cavity of the lung is divided into a honeycomb of chambers, separated by projecting septa of epithelial-covered connective tissue.

It might also be supposed that, as the result of intra-uterine disease, or the influence of maternal syphilis, an overgrowth of the fibrous elements of the mesoblastic tissue, into which the primary pouches grow, may occur. The resulting fibrosis would cause compression and obliteration of the terminal ramifications of the secondary and tertiary diverticula and distension of the smaller bronchioles and infundibula after birth with each act of respiration.

After a certain time the malformed lung would become converted by progressive dilatation of the bronchi and bronchioles into a mass of tissue honeycombed with cysts of various sizes. These may at first communicate with a more or less dilated bronchus, or eventually become entirely shut off from it and each other. The extent to which this condition is compatible with life will naturally depend on the amount of lung-tissue left.

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*December 5th,* 1905.

## 20. *A study of cytodiagnosis: with special reference to its application in clinical medicine.*

By E. Athole Ross.
(From the Louis Jenner Clinical Laboratory, St. Thomas's Hospital.)

(With Plates III and IV.)

### Introduction.

It is chiefly with a view to investigate the value of cytological methods as an aid to the early recognition of tuberculosis that the present research has been undertaken.

But since pathological fluids containing cells occur under such widely divergent conditions, it is hardly desirable to treat the subject of cytodiagnosis in so restricted a way as would be necessitated by the consideration of any one particular disease.

Having regard, therefore, to this difficulty, I have included under separate headings:

(1) Pleural effusions due to micro-organisms other than the tubercle bacillus and cerebro-spinal fluids from cases of meningococcic infection.

(2) Ascitic fluids.

(3) Hydrocele fluids.

In the vast majority of the instances in which the cerebro-spinal fluid was examined the lesion was due either to the tubercle bacillus or to the meningococcus, while certain of the examples of pleural effusion and vaginal hydrocele occurred in the course of malignant disease. This latter variety of case has also been dealt with separately.

It will scarcely be disputed that cytodiagnosis finds its most valued application in the detection of tuberculous disease for the two following reasons:

(1) The tubercle bacillus is difficult to cultivate.

(2) This micro-organism, when present in serous pleural effusions, is only to be found in such small numbers that it is necessary to examine bacteriologically very large quantities of fluid, and even then with possibly negative results.

At present (since an examination of the sputum is often without value in cases of primary pleurisy) almost the only reliable means at our disposal of demonstrating the tubercle

bacillus under these circumstances is by intra-peritoneal inoculation of the fluid into guinea-pigs. This test is quite satisfactory, but it will always be open to the objection that a period of some six weeks may have to elapse before an absolute diagnosis is possible.

On the other hand, a complete histological examination of the cells present in an effusion can be made and a report returned in a few hours.

Before it is safe to assert that a preponderance of small lymphocytes in a pathological fluid points to tuberculosis it is obviously necessary to confirm such a statement in every way possible.[1] None of the cases in the present series are classified as undoubtedly tuberculous unless at least one of the three following conditions has been fulfilled:

(*a*) That the sputum (when obtained) contained tubercle bacilli.

(*b*) That tuberculosis was produced experimentally by the inoculation of the suspected fluid into a guinea-pig.

(*c*) That *post-mortem* evidence of tuberculosis was forthcoming.

Although Widal and Ravaut, the pioneers in this field of work, and many other writers were careful to confirm their results by every means in their power, the literature shows some tendency to ignore the importance of inoculation experiments. Certain authors do not state definitely that they have made use of animals, and in a few instances the papers appear to be mere compilations of work by previous observers.

With these preliminary remarks I shall now proceed to take a short bibliographical survey of the subject.

## The Literature of Cytodiagnosis.

In the comparatively short space of five years some forty monographs dealing with the subject of cytodiagnosis have appeared, and although the most important contributions are by French authors, reliable work has also been done in Great Britain, the United States, and Germany. It should be noted that priority in the application of cytodiagnosis is claimed by

[1] Widal's conclusion, supported by Abadie and others, that the cytology of any given case is only of value as differentiating an acute from a chronic lesion, will be discussed elsewhere.

Lewkowicz for certain Polish observers,[1] who stated that serous effusions, which do not become purulent, contain lymphocytes, but if polymorphonuclear cells are found, either pus-formation or cancer is present. In 1897 Warthin published a case of primary spindle-celled sarcoma of the pleura, which was diagnosed by a cytological examination of the fluid obtained, and consequently this author may claim a place among the earlier writers.

No further advance was made until June, 1900, when Widal and Ravaut published one of their series of papers in the Journal of the Société de Biologie, and to them is certainly due the credit of having been the first to demonstrate conclusively the relation that exists between clinical diagnosis and the cytology of pathological fluids. As the result of their investigations these writers stated their so-called cytological formulæ, which they regard as applying to the cells found in the different effusions they examined.

If we consider how extensive the literature of cytodiagnosis has become, it is indeed surprising that so little new matter should have been added since this original article was published. Owing to the extreme importance of the work done by Widal and Ravaut I have thought it best to give a brief summary of their papers and afterwards to record any additional facts which are due to other observers.

"*Applications cliniques de l'étude histologique des epanchements sero-fibrineux de la Plèvre.*" *Widal and Ravaut.* '*Soc. Biol.*,' *June* 30*th*, 1901.

The authors remark on the constancy of the lymphocytosis in cases of so-called idiopathic pleurisy with effusion. By inoculation tests in such cases they infected 71 per cent. of guinea-pigs with tuberculosis. They state that if the fluid be examined very early in the course of the disease, a few (2 per cent. to 10 per cent.) finely granular polynuclear cells may be present, but that these are shortly replaced by small lymphocytes. In these examples endothelial cells were rare. They obtained positive results also from cases of pneumothorax and from tubercular cases with advanced lesions.

[1] Winiarski, 'Kronika lekarska,' 1896; Korczyriski and Wernecki, 'Przeglad lekarski,' 1891.

In "mechanical effusions" due to cardiac, renal, or malignant disease the endothelial cell predominated and was sometimes found to be phagocytic for red corpuscles and white cells. As evidence that the endothelial cells were rubbed from the surface of the serosa they mention the presence of "placards" in which the outline of the individual cell was lost. They consider that no endothelial cells would occur in tuberculosis because the newly formed tuberculous membrane would prevent desquamation. Although finely granular polymorphonuclear cells and an excess of endothelial cells pointed to a mechanical effusion, small lymphocytes might be present. The inoculation experiments produced negative results.

One case of special interest is cited in which a sero-fibrinous effusion appeared in a case complicated with softening at one apex: numerous small lymphocytes and typical endothelial cells were present in placards. Two inoculation experiments in this instance proved negative.

Under another heading they discuss the acute infective pleurisies and in a streptococcus example they obtained degenerated polymorphonuclear cells in large excess. In pneumococcus pleurisy this cell again predominated, but large mononuclear cells (possibly of endothelial origin) were observed englobing both the polynuclear and the red cells.

They group three cases of eosinophile pleurisy together, noting that these were from different sources of infection. In all the eosinophilia was more marked in the effusion than in the blood. This fluid when inoculated into guinea-pigs proved to be very toxic.

"*Cytodiagnostic de la méningite tuberculeuse*," *Widal, Sicard and Ravaut.* '*Presse Médicale*,' *October* 17*th*, 1890.

In this communication the authors have turned their attention to the cytology of the cerebro-spinal fluid under certain morbid conditions.

They give a series of twelve cases of tuberculous meningitis, confirmed by autopsy. The cerebro-spinal fluid was sometimes blood-stained or cloudy and at others limpid and very like the normal. In these examples small lymphocytes were always in excess even when a large amount of blood was present. They admit that the finely granular polynuclear cells are more numerous here

than in pleural effusions of tuberculous origin, but consider that a moderate number of these cells does not affect the diagnosis provided that the small lymphocytes predominate. They emphasise this point by an interesting series of experiments on dogs.

A culture of tubercle bacilli from man was injected beneath the meninges, and in one case, examined on the eighth day, the proportion of the finely granular polymorphonuclear cells to the small lymphocytes was 40 to 60, but on making a second examination four days later this ratio had become 28 to 72.

In two cases of cerebro-spinal meningitis the fluid contained very many finely granular polymorphonuclear cells, while small lymphocytes only occurred at rare intervals. In two cases of hæmorrhagic pachymeningitis the polynuclear cells occurred in large numbers among the red corpuscles and only a few small lymphocytes were present.

Returning to experimental work, the writers injected two dogs beneath the meninges with the pneumococcus, and in each instance found finely granular polymorphonuclear cells present in large excess. Similar experiments with the *Bacillus typhosus* produced a cell picture consisting almost entirely of polynuclears.

They state that in tuberculous cases the finely granular polymorphonuclear cells were always less numerous than the small lymphocytes, and that in all doubtful cases a differential count would settle the question.

Summing up the advantages of cytodiagnosis, they point out that cultural methods are unsatisfactory, and that it takes some weeks to obtain a diagnosis by inoculation experiments.

*"A Propos du Cytodiagnostic du Tabes," Widal, Sicard and Ravaut. 'Revue Neurologique,' No. 6, March 30th, 1903.*

In the first part of this paper the authors reply to MM. Armand-Delille and Camus, who have questioned the accuracy of cytological methods as applied to diagnosis. It is urged, in answer to these criticisms, that errors of technique are responsible for their results. It is pointed out that the writers, in conjunction with Monod, have found a marked lymphocytosis of the cerebro-spinal fluid in cases of tabes, and Babinski is quoted as having had some 97 per cent. of similar results. The following extract is important:

"The lymphocyte in the cerebro-spinal fluid is no more a

specific element of tabes or general paralysis than it is of tuberculosis; it is merely to be regarded as an indication of a simple irritative process. The finely granular polynuclear cell, when occurring alone, betrays by its presence a congestive or inflammatory state, for it could only be derived from the blood-vessels by a diapedesis."

The authors found a lymphocytosis in syphilitic meningitis, meningo-myelitis, and hemiplegia. In hemiplegic cases of doubtful origin they claim that this is of importance, for when the lesion is due to cerebral hæmorrhage or to softening there is no persistent lymphocytosis, although a discrete and evanescent one may occur immediately after the stroke.

Positive results were occasionally obtained in tertiary lesions without involvement of the nervous system (three cases of ulceration of the soft palate), and a lymphocytosis was also found in two cases of severe secondary syphilis with persistent headache. In cases of cerebral tumour not involving the meninges cytological examination proved negative, and no cells were present in the cerebro-spinal fluid in hysteria, neurasthenia, epilepsy, or classical polyneuritis.

They note that in certain cases of herpes zoster and of sciatica a lymphocytosis occurred, but show that it was absent in typhoid fever and erysipelas.

In conclusion, the writers state that Roget and Esmonet have proved lymphocytosis to be absent in variola with cerebral complications, but that Monod has demonstrated its presence in 43 per cent. of cases of mumps, in which the virus seems to have a predilection for the meninges.

"*Les Albumines de liquide céphalo-rachidien au cours de certains processus méningés chroniques. Widal.* '*Revue Neurologique,*' 1903.

This article deals with the chemistry of the cerebro-spinal fluid in health and disease. Widal remarks that chemical methods could not be applied so as to take the place of cytodiagnosis.

"*Some Experimental Work on Lumbar Puncture of the Subarachnoid space.*" *H. Wentworth.* '*Archives of Pediatrics,*' 1896, *p.* 567.

This paper is of interest as it is one of the earlier records in the literature of the subject.

Wentworth noted that the cerebro-spinal fluid was often cloudy, and showed microscopically that this was due to the presence of cells. He states that he found cells resembling lymphocytes in the tuberculous cases, but in examples of pyogenic origin the finely granular polynuclear cell predominated. He concludes that the most satisfactory method of proving a lesion to be tuberculous is by inoculation experiments.

"*The Diagnosis of Primary Sarcoma of the Pleura from the Cells found in the Pleuritic Exudate.*" *A. S. Warthin.* '*Medical News,*' *October* 16*th*, 1897.

The author considers this neoplasm to be an hæmangiosarcoma, and that it should be classed among the endotheliomata. Its origin was from the mediastinal pleura. On staining films of the exudate with methylene blue numerous small spindle cells were found, and by cutting sections from hardened portions of the sediment he established the presence of very numerous mitoses. He gives a differential table for the distinction of sarcoma cells from fibroblasts, and believes that the occurrence of mitosis is the most important point in malignant cases. The writer is also responsible for the statement that in the exudate from tuberculous cases endothelial cells and fibroblasts occur alone. His examination, however, was made after death, and the lesion was apparently not a recent one.

"*The Cytology of Serous and Serofibrinous Effusions of the Pleural and other Serous Cavities and of the Cerebro-spinal Fluid.*" *H. C. Earl.* '*Dublin Journal of Medical Science,*' *December*, 1903.

This paper contains an excellent review of the work done on cytodiagnosis up to the date of its publication. Dealing with malignant disease, the author remarks that in effusions due to carcinoma of the serous membranes cancer-cells may be absent, but are occasionally undoubtedly present. Wolf and Quincke have drawn attention to the confusion that may arise in such cases between neoplastic and endothelial cells. It is stated that the former often contain glycogen, while the latter only rarely react to iodine, and that mitosis is greatly in favour of neoplasm. Dr. Earl is also fully alive to the errors which may occur if

degenerated cells are counted, and refers to the so-called "pseudo-lymphocyte." Widal's work on the cytology of hydrocele fluid is also summarised as follows: (1) In chronic cases of old standing the cells, when found, consist entirely of the endothelial variety. (2) In hydroceles due to the gonococcus or to the tubercle bacillus the finely granular polymorphonuclear cell or the small lymphocyte is present according as the infection is gonorrhœal or tuberculous.

"*On the Value of the Examination of the Cerebro-spinal Fluid in the Diagnosis of Nervous and Mental Diseases.*" *E. Siemerling.* '*Berliner klinische Wochenschrift,*' *May,* 1904.

From his own work on cytodiagnosis this writer is led to accept the statements of previous writers, and he insists on the value of lymphocytosis as an aid in distinguishing organic from functional disease.

In a case of cerebral tumour he obtained a negative result, and suggests that a gummatous lesion is thus excluded. In cases of mental derangement no cells were found in the cerebro-spinal fluid.

"*Transudate and Exudate: their Morphology and the Distinction between them.*" *A. Wolff.* '*Zeitschrift für Klinische Medizin,*' 1901, *Band xlii.*

This observer believes that an excess of finely granular polynuclear cells is only to be found in exudates, while lymphocytes are confined to transudates. He considers that in a large number of instances of pulmonary tuberculosis we have to deal with transudates, and that this fact accounts for the absence of bacilli in most serous pleural effusions occurring under these circumstances. In exudates, on the other hand, micro-organisms are numerous.

"*The Cytodiagnosis of Pleural Effusions.*" *G. Lovell Gulland.* '*Scot. Med. and Surg. Journ.,*' *June,* 1902.

Dr. Gulland, referring to the difficulty of demonstrating tubercle bacilli in certainly the majority of cases, thinks it possible that the effusion may be due to the action of a toxin formed by the micro-organism. He found that in some instances of undoubted tuberculosis inoculation results were negative. He

agrees with Widal as to the interpretation of lymphocytosis in "idiopathic" pleural effusions and limits the initial prevalence of polynuclear cells to the first three days. In one example of effusion secondary to malignant disease of the lung only finely granular polymorphonuclear cells were found.

"*Cytodiagnostic et Méningite Tuberculeuse.*" *Marcou Mutzner.* '*Arch. Gén. de Médicine,*' *September,* 1901.

In this paper an attempt is made to refute the conclusions of all previous workers on the strength of a single example of miliary tuberculosis in which finely granular polynuclear cells were found to replace lymphocytes in the cerebro-spinal fluid.

"*Resultats de l'examen cytologique des quelques liquides céphalo-rachidiens.*" *M. J. Abadie.* '*Soc. Biol.,*' 1902, *p.* 946.

Abadie's work goes far to confirm the results previously obtained by other observers. Some instances, however, are of special interest. He obtained a negative result in two cases of old organic hemiplegia and also in one example of cerebral tumour with double optic neuritis. On the other hand, he found that the cerebro-spinal fluid in an intra-cranial neoplasm, due to hydatid disease, contained a few normal small lymphocytes. The following passage is worthy of quotation:

"These results go to confirm the rule, long ago laid down, that the occurrence of a lymphocytosis in the cerebro-spinal fluid indicates an organic change in the cerebro-spinal meninges. The variations of the leucocytes do not 'translate' the nature of the meningeal irritation; they cannot serve to affirm such and such a disease, but are rather to be taken as a test of an acute, subacute, or chronic morbid process."

"*The Treatment of Tuberculous Pleural Effusion and Pneumothorax.*" *Professor W. Osler.* '*British Medical Journal,*' *October* 15, 1904.

Professor Osler in this paper refers to several points of special importance in estimating the value of cytodiagnosis.

(1) Eichorst has shown that by using large quantities of the exudate, or the centrifuged sediment, 65 per cent. to 85 per cent. of positive results were obtained by inoculation.

(2) Hamman, working in Professor Osler's ward, found that eighty-six cases of pleurisy with effusion subsequently became tuberculous, and that of these 34·8 per cent. died of phthisis.

(3) The tuberculin reaction gives assistance in doubtful cases.

"*A propos des Hydrocèles. Cytologie; Inoculations; Resultats.*" *Barjon et Cade.* '*Archiv Gén. de Méd.*,' 2, 1903.

These authors emphasise the frequency with which spermatozoa occur in hydrocele fluid. Inoculation tests are the only reliable means of determining whether the simple "idiopathic" hydrocele is tuberculous. Having obtained ten negative results —a total of 100 per cent.—they conclude that the tubercle bacillus has no part in the pathology of such hydroceles.

"*The Cerebro-spinal Fluid in relation to Disease of the Nervous System.*" *F. W. Mott.* '*Brit. Med. Journ.*,' *December 10th*, 1904.

Dr. Mott accepts the findings of Widal, Ravaut, Sicard, and others; he believes that in the majority of cases the absence of lymphocytosis points to functional disease. He considers the presence of macrophages in the cerebro-spinal fluid to be diagnostic of hæmorrhage. For red cells are only found under these conditions, and the phagocytic macrophages are then derived from the endothelial cells which line the subarachnoid space. His remarks on the occurrence of lymphocytosis in the cerebro-spinal fluid during sleeping sickness are of special interest; he says: "It is my opinion that the lethargy is due to cerebral anæmia, caused by compression of the small vessels owing to an accumulation of large and small lymphocytes in the perivascular spaces." He points out that this would cause a mechanical interference with the circulation. He does not unreservedly accept the trypanosome as the cause of the malady, but holds that the general glandular enlargement which occurs in these instances is related to the obstruction of the cerebral vascular system by lymphocytes. The macroscopic lesion is that of chronic meningo-encephalitis.

"*Eosinophile Pleurale.*" *Barjon et Cade.* '*Archiv Gén. de Méd.*,' *August*, 1903.

They conclude that the cytology of ascitic fluid is too variable to be of value. In two cases of alcoholic cirrhosis and in one

example of ovarian cyst they found an excess of endothelial cells with a few small lymphocytes. In two cases of tuberculous peritonitis small lymphocytes predominated. In two instances of carcinomatosis of the peritoneum small lymphocytes, in others endothelial cells were observed.

Their remarks on eosinophile pleurisies must be given in some detail.

If the coarsely granular polynuclear cells exceed 10 per cent. the effusion is to be regarded as eosinophilic. In such examples eosinophilia in the blood was found to be variable.

In their five cases Barjon and Cade found:

(1) The amount of the fluid was always small.

(2) The greatest number of eosinophiles present in any one case was 35 per cent.; at a second count this was reduced to 8 per cent., and finally this type of cell gave place to the small lymphocyte. In another instance, however, the coarsely granular polynuclear cells were gradually replaced by finely granular polymorphonuclears.

(3) They conclude that pleural eosinophilia may be seen when there is no suspicion of tuberculosis, and have observed it in simple hydrothorax. In doubtful cases the infection, if present, is invariably of a mild type.

(4) The inoculation test proved negative in all of their five examples.

"*The Cytodiagnosis of Pleural and Cerebro-spinal Fluids.*" *Edward Turton.* '*Practitioner,*' *April,* 1905.

This writer gives his technique fully and notices the difficulties which may arise from the presence of degenerated cells. He does not record any inoculation experiments, but his interpretation of the various cytological formulæ is based on personal experience and is in accord with that of most observers. The value of this paper is greatly increased by the full bibliographical references given in the foot-notes.

'*Cytodiagnostic du Liquide. Céphalo-rachidien dans quarantecinq cas d'Affections Nerveuses et Mentales.*" *Par MM. Nageotte et Jamet. Soc. Méd des Hôpitaux, January 17th,* 1902.

Out of 36 cases of epilepsy negative results were obtained in 35. In the remaining example a lymphocytosis was found,

but there was more than a suspicion of congenital syphilis. In 5 cases of General Paralysis of the Insane lymphocytes were absent in only 1 instance. This latter example was a peculiar one in that the mental symptoms had remained stationary over a period of five years.

In the discussion that followed this paper Widal remarks: "We must never lose sight of the fact that in the normal cerebro-spinal fluid two or three small lymphocytes are always to be found per field of the oil immersion lens. To diagnose lymphocytosis these elements must be sufficiently numerous to cause no hesitation."

"*Examen Cytoscopique du Liquide Cëphalo-rachidien dans la Sclérose en Plaques.*" *Par M. G. Carrière.* '*Soc. Biol.,*' *March,* 1901.

In three examples the cerebro-spinal fluid contained an excess of small lymphocytes. In a case of hysteria, which simulated disseminated sclerosis, the author obtained a negative result. This fact is considered to be of great significance, as the differential diagnosis is frequently very hard.

"*Note sur l'étude Cytologique des Epanchements de Diverses Séreuses.*" *Par MM. Dopter et Tanton.* '*Gazette des Hôpitaux,*' *July,* 1901.

The results obtained by these writers are, in the majority of instances, confirmatory of previous work. In a case of tuberculous peritonitis they found small lymphocytes almost exclusively. One or two examples are, however, anomalous; thus, in a case of chronic hydrocele of six years' standing, with enormous thickening of the tunica vaginalis, the small lymphocyte predominated. Syphilitic disease and tuberculosis appear to have been carefully excluded, and sections from the sac wall were examined histologically. In hydroceles complicating tuberculous epididymo-orchitis they obtained the small lymphocyte in every instance. The strangest result occurred in a case of ascites due to cirrhosis of the liver, in which the finely granular polynuclears were not only present, but actually outnumbered the lymphocytes and endothelial cells taken together.

"*Contribution à l'Étude du Cytodiagnostic du Liquide Céphalo-rachidien dans les Affections Nerveuses.*" *Babinski et Nageotte.* '*Soc Méd des Hôpitaux,*' *May,* 1901.

These writers examined seven cases of cerebral tumour with a negative result; they conclude that a lymphocytosis does not exist in cerebral neoplasm, and consider this of interest because such tumours frequently light up a meningitis. The further hypothesis that a meningitis may cause no alterations in the cytology of the cerebro-spinal fluid is certainly open to question.

It was found that lymphocytosis failed in cases of circumscribed, as distinct from diffuse, syphilitic infection, and it was maintained that a permanent lymphocytosis, when not associated with tuberculous infection of the meninges, always revealed diffuse syphilis.

*Gumprecht:* '*Deutsche medicinische Wochenschrift,*' *June,* 1900.
*Ossipow:* '*Deutsche Zeitschrift für Nervenheilkunde,*' *April,* 1901.

These papers only deal with the operative risks in lumbar puncture.

*Laignel-Lavestine:* '*Soc. Biol.,*' *May,* 1901.

This article gives an account of a method for determining the exact number of cells per c.mm. in the cerebro-spinal fluid.

*Tarchetti and Rossi:* '*Gazetta degli Ospedali,*' *No.* 102, 1902.

These authors found that the endothelial cells present in transudates were associated with small mononuclear cells in large numbers. These latter are said to differ from true lymphocytes and to be modified endothelial cells. On the other hand, they considered that true lymphocytes were found in primary pleurisies of tuberculous origin.

"*Ueber Cytodiagnostic der Ex- und Transudate,*" '*Deutsche med. Wochenschrift,*' *vol. xxviii, No.* 16, 1902.

Patella believes that in "idiopathic pleurisies" the lymphocytes are really the free nuclei of endothelial cells, and states that he has watched the progress of the changes in these cells up to the time at which the free nuclei are found. He considers that "pseudo-lymphocytes" may be found in any condition in which endothelial cells are cast off in large numbers.

*Marcel Labbé: 'Le Cytodiagnostic,' Paris,* 1903.

In connection with the cytology of neoplasm Labbé and others have described very large round or oval cells with large nuclei and granular protoplasm with some vacuolation, which they regard as distinctive of sarcomatous effusions.

*Bernheim and Moser: 'Berliner klinische Wochenschrift,' p.* 468, 1897.

This reference is of interest as one of the earliest notices of the fact that the cerebro-spinal fluid in tuberculous meningitis contains an abundance of lymphocytes.

*G. Lambelli: 'Il Morgagni,' September,* 1904.

Lambelli maintains that a differential diagnosis cannot be based upon a leucocyte count alone. In eleven examples of tuberculous meningitis he found a lymphocytosis, but was unable to find the tubercle bacillus. In other instances due to the pneumococcus the finely granular oxyphile cells amounted to about 40 per cent.

*"De la valeur clinique du cytodiagnostic céphalorachidien dans les cas douteux de paralysie générale." Maillard. 'Thèse de Bordeaux,'* 1901.

The findings of this author in the cerebro-spinal fluid of general paralytics agree entirely with those of previous observers.

*Neider and Mamlock: 'Zeitschr. f. klin. Med.,' H.* 1 *and* 2.

These authors have investigated the cerebro-spinal fluid in cases of nervous disease. The examples quoted are to some extent anomalous:

(1) In a case of severe secondary syphilis, unaccompanied by nervous manifestations, a striking increase in the number of lymphocytes was found.

(2) In an instance of uræmia with convulsions a moderate lymphocytosis occurred.

(3) Two cases of tetanus were positive, one being associated with a large number of polymorphonuclear leucocytes.

Although meningeal irritation has been assumed as the cause of lymphocytosis, Neider and Mamlock urge that it is not the only factor of importance. They believe that intoxication plays an important *rôle* "when there is a continued irritation of the

central nervous system by a constantly developed or continuously renewed virus." They consider that this explains the positive results in syphilis, tetanus, and uræmia, and the negative results in epilepsy, hemiplegia, and coma. They also believe that a constant mechanical irritation may cause a lymphocytosis. There was a very striking increase of lymphocytes in one case of brain tumour and in another of a cervical cord tumour, neither of which were syphilitic. In two rabbits small air-balloons were introduced beneath the skull to simulate the presence of tumours, and in both there was produced a moderate but definite lymphocytosis.

"*Cytology of Pleural Effusions.*" *Vargas-Saurez.* '*Beiträge zur klinik der Tuberkulose,*' 1904, *Band ii, p.* 201.

In fifteen cases of idiopathic pleurisy lymphocytes were in large excess. Two examples—one of tuberculous, the other of rheumatic origin—were nearly free from cells. In two instances the author was able to make a certain diagnosis of carcinoma by the discovery of tumour-cells in the exudate. He considers that the majority of the lymphocytes occurring in pleural effusions are true lymphocytes, derived by actual migration from the blood- or lymph-vessels. They are not degeneration products of endothelial cells, nor are they lymphoid cells derived from the fixed tissues.

### Technique.

During this research investigations were made into the nature of the cells present in (*a*) pleural, (*b*) ascitic, (*c*) cerebro-spinal, and (*d*) hydrocele fluids. With two exceptions, all the material for cytological examination was obtained from cases under treatment in St. Thomas's Hospital.

A specimen of fluid sent for examination was treated as follows: Two large tubes, each holding 50 c.c., were centrifuged at moderate speed to insure that all the cellular elements should be driven down into the sediment. The importance of using a moderate speed lies in the fact that the force generated by a high velocity causes the cells to disintegrate, and consequently failure to take this precaution leads to inaccurate results. Special care was directed to the sterilisation of all glass vessels with which the fluid came into contact. Film preparations were

made by smearing a loop of the sediment on to a clean coverslip. At this stage it was important to avoid damaging the cells by the exertion of undue pressure, and it was also essential to be certain that the loop of fluid contained some of the clot lying at the bottom of the tube which had entangled the cells in its meshes.

Films thus prepared were then dried in air and stained by a rather weaker solution (0·3 per cent.) of Leishman than is suitable for hæmatological work (0·5 per cent.). The stain was poured on to the coverslip and allowed to remain for thirty seconds to fix the film; double the volume of distilled water was added for seven minutes, after which the excess of stain and water were removed. Finally the film was covered with distilled water for a further period of two minutes, cleansed, dried between cigarette-paper, and mounted in Canada balsam. It must be remembered that the above time limits are only approximate, as they vary somewhat with each freshly prepared sample of stain.

In every instance, when possible, a differential count of 500 cells was made under the one twelfth oil immersion lens, and the fluid was also chemically examined in many cases.

*Inoculation experiments.*—Since the utility of cytodiagnosis must be judged by the results of bacteriological investigation, any work on this subject undertaken without inoculation experiments can have no value. Of course the above statement is not applicable to those cases in which *post-mortem* evidence of tuberculosis, etc., is forthcoming.

One hundred c.c. of fluid were centrifuged at high speed to drive all micro-organisms to the bottom of the tubes, and from fifteen to twenty c.c. of the lower layers used. The inoculation was made into the peritoneal cavity of a guinea-pig with the same precautions to secure general asepsis and to avoid contamination from external sources as were adopted by Dudgeon and Ross in their work on phagocytosis. After five weeks or more the animal was killed under chloroform and a complete *post-mortem* examination made.

*Post-mortem examination.*—All the organs were examined for macroscopic evidence of disease, especial attention being directed to the spleen and great omentum. In addition film preparations, stained by Leishman, were made from the peritoneal fluid

and 500 cells enumerated as described above. Smears were also taken on slides from the retroperitoneal lymphatic glands and stained for tubercle bacilli. This is a point of extreme importance, as will appear later. Finally a routine histological examination was undertaken in every instance. Paraffin sections were cut from the spleen and lymphatic glands and out of a large number of stains tried for these hæmatoxylin, with eosin as a counter-stain, was found to act best. In many cases the liver, kidneys, lungs, and anterior mediastinal glands were also cut and searched for evidence of tuberculosis. The importance of confirming macroscopic appearances by histological examination cannot be over-estimated, as more than one example occurred in which the naked-eye evidence of tuberculosis was equivocal. In conclusion, it is hardly necessary to state that damage to micro-organisms was prevented by cooling all sterilised vessels immediately previous to use.

## On the Significance of the Small Lymphocyte in Pathological Fluids.

Before discussing those cases in my series which were characterised by a predominance of the small lymphocyte some mention must be made of errors due to failure in differentiating the various types of cell present, and it will also be necessary to state the reasons for one or two special precautions in technique.

Writing in the 'Practitioner' on cytodiagnosis, Dr. Turton pithily observes: "It is probably owing to failure in recognising some of these degenerate forms that certain of the discordant results obtained in cytology are to be accounted for."

If the worker in this branch of pathology is unable to recognise with certainty the cells present in any given case, his results will be valueless. It is an unquestionable fact that if a pleural effusion or other pathological fluid be allowed to stand for more than two or three hours the cells begin to disintegrate and rapidly become degenerated beyond recognition. Lovell Gulland suggests that degenerated cells may be distinguished by Sudan III or Scharlach R, since fatty degeneration does not occur in the lymphocytes and the cells showing this reaction would not belong to that class.

This difficulty is at once overcome by examining for cells immediately after aspiration or lumbar puncture has been performed. It is much better to reject all unsuitable specimens than to allow mistakes to occur in this way.

Total or partial destruction of cells by centrifugation at too high a speed has already been referred to.[1]

In the literature there are numerous instances where the so-called "pseudo-lymphocyte" has caused doubt.[2] Although it is quite clear that Prof. Ehrlich fully realised the true nature of this element, yet it is most unfortunate that he should have employed such a term to designate a slightly aberrant type of the finely granular polymorphonuclear cell.

All authors are agreed that "pseudo-lymphocytes" are generally found associated with definite, finely granular, polynuclear cells, and are especially abundant in effusions approaching the purulent stage. The nucleus swells up, its outline becomes more nearly regular, and its distinctive character is less marked; the protoplasm fails to stain in the normal manner and the appearance of a mononuclear cell is more or less closely simulated.

It is further stated that portions of the nucleus with a zone of protoplasm are separated from the original cell and that the "pseudo-lymphocyte" is produced in this way.

In Case 21 (pulmonic neoplasm with pleural effusion) 21·8 per cent. of polynuclears occurred which were not degenerated and might have been mistaken for small lymphocytes under a sixth objective; with an oil-immersion lens, however, their true nature became at once apparent. The nucleus remains distinctly "polymorphous," except that its outline is more regular than usual, and the protoplasm differs in no way from that found in the finely granular polymorphonuclear of the blood. The only striking feature presented by the "pseudo-lymphocyte" is that the amount of this surrounding protoplasm has become reduced to a mere zone.

This atypical variety of polynuclear occurred (slightly degenerated) in two other examples of my series, while Dudgeon and Ross not infrequently found it present in the peritoneal exudate of guinea-pigs.

[1] See "Technique."

[2] Turton, Earle, and others.

If it were a rule to examine only films prepared from *fresh* fluid and to always count under an oil-immersion lens, the "pseudo-lymphocyte" would hardly ever escape detection or cause any trouble.

Patella adds to the confusion by using the term "pseudo-lymphocyte" in reference to the small lymphocyte almost constantly found in those primary "idiopathic" pleural exudates which we are about to discuss. He states that these lymphocytes are merely the cast-off nuclei of endothelial cells, and that he has seen this extrusion taking place. No confirmation of this view is to be obtained. I have occasionally seen an isolated endothelial nucleus, generally with a small tag of protoplasm attached, lying free in the field. Since such a nucleus, when stained by Leishman, in no respect resembles a lymphocyte, it is difficult to understand why this point was ever raised. In counts done on ascitic fluids it is common enough to see small endothelial cells, but here again with the high powers it is hardly possible to mistake such elements for lymphocytes.

It is also probable that the great variety of staining reagents used by authors (see "Literature") may account for some of the discrepancies; crude methylene blue, hæmatoxylin and eosin, and Ehrlich's triacid stain are by no means satisfactory. I believe that if Prof. Leishman's modification of the Romanowsky stain were exclusively used for this work, our cell-counts would gain in accuracy.

Passing on to some technical points, it will be found that Widal in his paper states that from 20 to 40 c.c. of an effusion must be injected into the peritoneal cavity of a guinea-pig, if positive results are to be insured. Lovell Gulland puts the limit at 70 c.c. and has waited thirteen weeks for a result.

It is certainly necessary to deal with large quantities of fluid owing to the scarcity of the tubercle bacillus in these cases, but nevertheless in practice this method has serious drawbacks. The animal becomes almost at once acutely ill and may die within a few hours. On examination no evidence of peritonitis can be found, but frequently a large quantity of unabsorbed fluid is present. It is probable that these ill effects are purely mechanical, and they have been successfully avoided in this work by using the sediment from 100 c.c. of effusion centrifuged at high speed.

TABLE I.

| No. | Nature of case. | Percentage of lymphocytes. | Result as to presence of tuberculosis. | How obtained. Remarks. |
|---|---|---|---|---|
| 2 | Pleural effusion | 49·8 | Not proved | No inoculation experiment. |
| 4 | „ | 97·6 | Positive | Inoculation experiment. This example shows the necessity for complete histological examination. |
| 5 | Meningitis | 93·0 | „ | Autopsy. |
| 6 | Pleural effusion | 92·4 | „ | Inoculation experiment. |
| 8 | „ | 83·2 | „ | Tubercle bacilli in sputum; signs at the right apex. Ten months later cough and cardiac pain were noted. |
| 10 | „ | 95·0 | „ | Inoculation experiment. |
| 11 | „ | 89·0 | Negative | Inoculation experiment. |
| 12 | „ | 90·8 | Not proved | No inoculation experiment. |
| 13 | „ | 86·6 | „ | Inoculation experiment. The animal died in 18 hours. |
| 18 | Hydrocele | 51·2 | Positive | Operation. Carious foci removed. |
| 27 | Meningitis | 77·0 | „ | Autopsy. |
| 29 | Pleural effusion | 87·0 | „ | Inoculation experiment. Tubercle bacilli in the sputum; signs at left apex. |
| 30 | „ | 73·6 | Not proved | No inoculation experiment. |
| 31 | „ | No cells seen | Positive | Inoculation experiment. Two animals used. |
| 34 | „ | 88·5 | Not proved | No inoculation experiment. |
| 36 | „ | 100·0 (very few cells) | Positive | Inoculation experiment. |
| 37 | „ | 100·0 (very few cells) | „ | Old standing lesion. Tubercle bacilli found. |

A reference to Table I will show that this plan has been attended with very constant results, and it is unnecessary to inject more than 10 c.c. Since using this method I find that Prof. Osler also refers to the advantages of centrifugation as a preliminary measure, but apparently this course has been adopted in only very few instances.

The importance of a complete autopsy in these animal experiments cannot be over-estimated. One example may be cited in which evidence of infection rested solely on the finding of four or five tubercle bacilli in a smear preparation from one of the retroperitoneal glands.[1]

In many instances the microscope will establish the presence of early lesions which must inevitably have escaped the most careful macroscopic scrutiny.

[1] Mr. L. S. Dudgeon has recently had a precisely similar experience.

Table I gives the results obtained from seventeen examples in which the small lymphocyte was the principal cell. In those cases classed as "not proved" it was either impossible to perform an inoculation experiment or the guinea-pigs died at an early stage. The numbers in the table refer to the order in which the cases were obtained, and are not consecutive. It will be observed that in fourteen examples the percentage of small lymphocytes is very high, and that the presence of other varieties of white corpuscles is fully accounted for by blood-contamination. In such primary tuberculous cases, confirmed by inoculation, tuberculin injection, or autopsy, Widal and Ravaut found lymphocytosis almost exclusively. Finely granular polynuclear cells, if present, are often less than 10 per cent.

Positive evidence of tuberculosis was obtained in eleven out of twelve of my cases which were tested by inoculation experiments or otherwise, and this amounts to 91·6 per cent.

If the individual examples in this table be examined the following points are of interest.

In Case 2 (49·8 per cent. of small lymphocytes) the cytological count did not appear to point to tuberculosis; since, however, no animal was inoculated this instance must be taken as wanting proof. There was in addition 32·4 per cent. of endothelial cells present, some showing mitotic figures. The patient made a complete recovery and reported herself quite well eleven months later. Widal quotes a somewhat similar case of sero-fibrinous effusion complicated with signs of softening at one lung apex. He found numerous small lymphocytes and placards of endothelial cells. Two guinea-pigs inoculated with 20 and 40 c.c. of the fluid proved negative in this instance.

Case 4 has already been referred to; it shows the great importance of searching for tubercle bacilli in smears made from the retro-peritoneal, iliac, and lumbar glands, and from the spleen before the guinea-pig is passed as not infected.

In Case 11, with 89·0 per cent. of small lymphocytes, the most careful and complete examination of the animal failed to show any evidence of tuberculosis. I prefer not to attempt to explain this result away by postulating an error of technique, although it would be a fair contention.

Case 13 is one in which the test failed owing to premature death of the animal used for inoculation.

The only example of hydrocele in this series (No. 18) was proved at operation to have complicated a tuberculous epididymitis. In this instance the percentage of lymphocytes was only 51·2. Dopter and Tanton in tuberculous hydrocele fluids found small lymphocytes in large excess. It must be admitted that a higher percentage than this should occur in pleural effusions in order to justify a diagnosis of tuberculous disease, but, as I shall presently show, these lower percentages occur in the cell counts of animals which have been infected with tuberculosis by the intra-peritoneal route. It appears that a lymphocytosis is more readily produced in some serous cavities than in others; since, however, this is an isolated example it would be useless to base any general conclusions on such evidence.

Case 31 is of special importance as illustrating what has already been stated as regards the rapid disintegration of the cells in these fluids. Here thirty-six hours had to elapse before the fluid could be examined, and by mistake it was centrifuged in the routine manner. Only a granular detritus was obtained. Two samples of this exudate were injected into the peritoneal cavities of a pair of guinea-pigs in order to gauge the relative toxicity of the upper as opposed to the lower layers of 100 c.c., which had been centrifuged at high speed to obtain the micro-organisms. The animal inoculated with the sediment developed obvious macroscopic tuberculosis in fifty-six days, while, as far as could be ascertained by naked-eye examination, the other was not diseased. Nevertheless, under the microscope early tuberculous lesions were detected in the spleen (see notes of case), and tubercle bacilli were found in smear preparations made from the retroperitoneal glands. The value of centrifugation as a preliminary to intra-peritoneal inoculation is thus well shown. A few very degenerated lymphocytes were seen in films prepared direct from the pleural fluid, but in the table cells have been returned as absent. One or two other examples of this type occurred, but they were rejected as unsuitable for further experiment, because the cells were not in good condition.

It is not possible on the strength of Case 31 to support the hypothesis that primary tuberculous pleurisy may occur without the presence of cells in the exudate. As Widal has pointed out the case is quite otherwise in old standing lesions where the diagnosis is already certain. In such instances, too, Widal and

Ravaut have obtained positive results in animals, but, on the whole, authors are agreed that it is harder to produce experimental tubercle under such conditions. I have but a single example[1] of this class in my series, and it was obtained from the Brompton Hospital. A few small lymphocytes in a good state of preservation were found in the pleural exudate, and an inoculation experiment was performed. The animal died three days later, without affording me any opportunity of following up the result in an undoubted instance of tuberculosis which had been slowly progressive for some years.

According to Widal the normal cerebro-spinal fluid contains two or three small lymphocytes per field of the oil-immersion lens, but Nageotte, Babinski, and Jamet all comment on the great scarcity of cells in the normal state. It is not easy to dispose of this difficulty, for any opportunity of examining the human cerebro-spinal fluid apart from disease rarely occurs in Great Britain.

Only two cases of tuberculous meningitis (proved at autopsy) are included in Table I, and the cytology of the cerebro-spinal fluid in both differed in certain respects from the formula of Widal and Ravaut.

These authors, as the result of numerous careful observations and experiments, find that in tuberculous meningitis relatively large numbers of polynuclear cells frequently occur, but that even in blood-stained specimens of fluid the small lymphocytes are always in excess. They further urge that a comparatively high percentage of polymorphonuclears mixed with the lymphocytes does not invalidate the diagnostic importance of the mononuclear elements, although a differential count may be needed to establish the excess of the latter cells. In my cases the lymphocytes predominated, but were not numerous, and polymorphonuclear cells occurred but rarely.

In neither instance was the full differential count of 500 cells possible, and the small lymphocytes amounted to 93 and 77 per cent. of the total cells present. Bernard found in one tuberculous case 140 lymphocytes (82·4 per cent.) and 30 polynuclear cells. Four days later there were 36 lymphocytes and 157 polynuclears. The increase in the polynuclears coincided with a secondary infection by pyogenic organisms, and this may be the

[1] See Table I, Case 37.

explanation of many of these cases. In five examples of tuberculous meningitis Bendix found the cells to be almost entirely small lymphocytes, while Turton in three instances obtained an excess of these cells averaging over 70 per cent. I may add that Mr. L. S. Dudgeon has noted a very marked predominance of lymphocytes in a number of cases examined. It will, therefore, be seen that the findings of many different observers do not absolutely agree with those of Widal in this respect.

TABLE II.—*The peritoneal fluid in the inoculation experiments.*

| No. of case. | Source of inoculated fluid. | Presence of tuberculosis. | Lymphocytes. | Endothelial cells. |
|---|---|---|---|---|
| | | | Per cent. | Per cent. |
| 4 | Pleural effusion | Positive | 53·6 | 45·6 |
| 6 | „ | „ | 82·2 | 11·4 |
| 10 | „ | Positive (very earliest stages) | 1·6 | 97·8 |
| 11 | „ | Negative | 2·8 | 97·2 |
| 13 | „ | Animal died in 18 hours | 21·6 | 75·0 |
| 29 | „ | Positive | 42·8 | 52·4 |
| 31 (pig. No. 1) | „ | Positive (massive tuberculosis) | 80·8 | 12·6 |
| 31 (pig. No. 2) | „ | Positive (the earliest stages) | 3 | 95·8 |
| 36 | „ | Positive | 44·2 | 54·4 |
| 37 | „ | Animal died in 3 days | 12·6 | 83·8 |

In Table II the percentages of lymphocytes and endothelial cells occurring in the peritoneal fluid of infected guinea-pigs are given. Here it is easy to obtain a normal standard for comparison. Dudgeon and Ross have recently examined the peritoneal fluid of several healthy guinea-pigs in order to determine the nature of the cells. In all cases but a small quantity of fluid could be obtained, and the chief cell was the endothelial. Lymphocytes numbered only 25 per cent. in a few examples, and in the vast majority were considerably below that figure. Hence it is fair to assume that a percentage of small lymphocytes higher than 30 is pathological.

Tarchetti and Rossi, writing on the endothelial cells present in transudates, remark that "these were associated with small mononuclear cells in large numbers, which latter differ from true lymphocytes and are modified endothelial cells. The lymphocytes found in primary pleurisy of tuberculous origin are true lymphocytes and not regressive phases of endothelial cells,"

## EXPLANATION OF PLATE III,

Illustrating the communication on "Cytodiagnosis," by Dr. E. A. Ross. (P. 361.)

FIG. 1.—Film preparation from a pleural effusion which was proved by inoculation to be tuberculous. It was obtained from a previously healthy male patient (Case 6), who had been ill for thirteen days before aspiration was performed. A differential count of 500 cells gave 92·4 per cent. of small lymphocytes. The white cells shown are exclusively of this variety. ($\frac{1}{6}$ obj.)

FIG. 2.—Film preparation from the peritoneal fluid of a guinea-pig which had been inoculated with 18 c.c. of the centrifuged fluid obtained from the above patient and killed at the end of forty-four days. It shows a high percentage (82·8) of small lymphocytes, and contrasts the nuclei of these with those of the endothelial cells. Note the open reticulum in the nuclei of the latter cells. ($\frac{1}{12}$ oil immersion obj.) In both cases Leishman's stain (0·3 per cent.) was used.

Red cells are of constant occurrence in these centrifuged fluids.

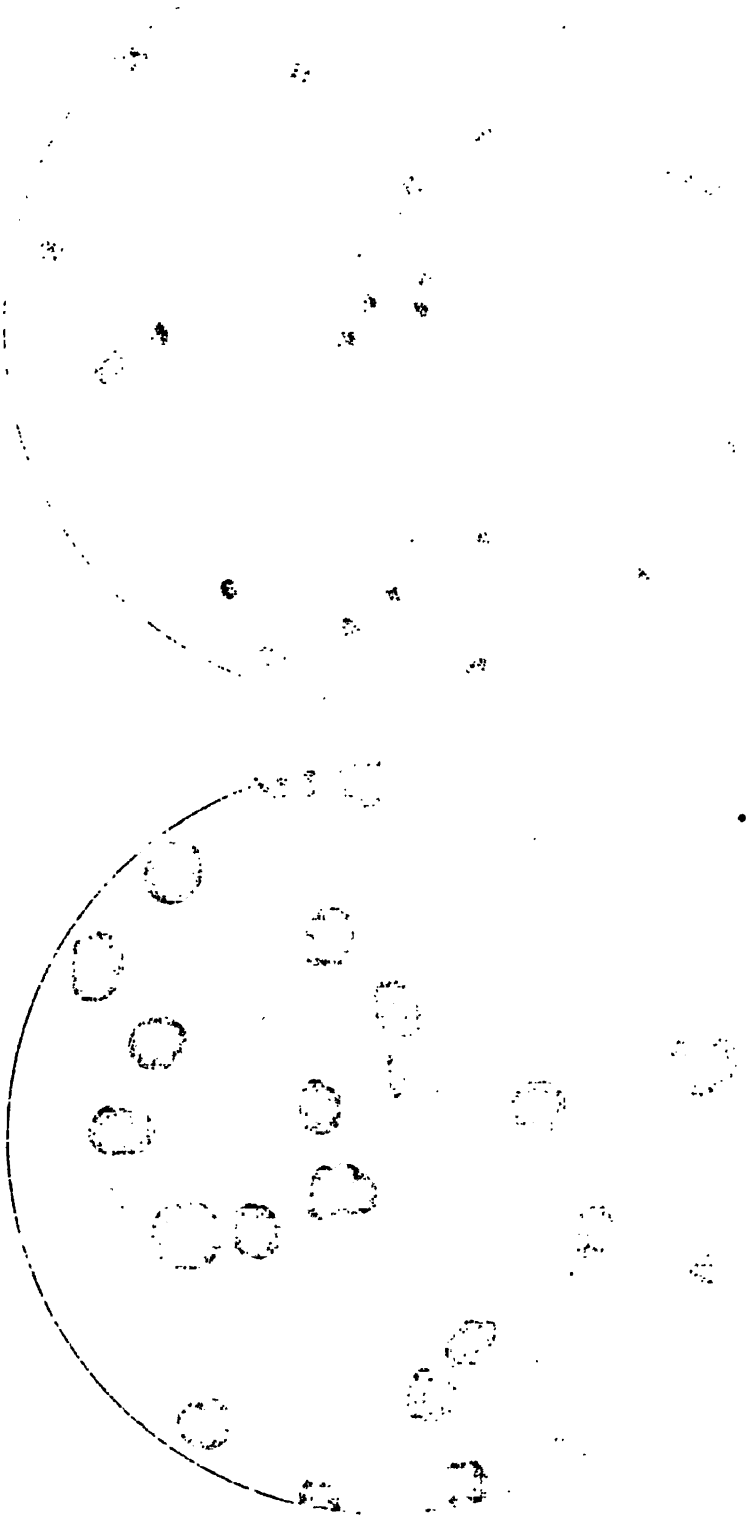
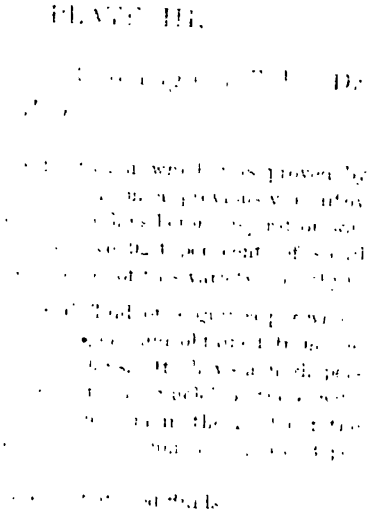


PLATE III.



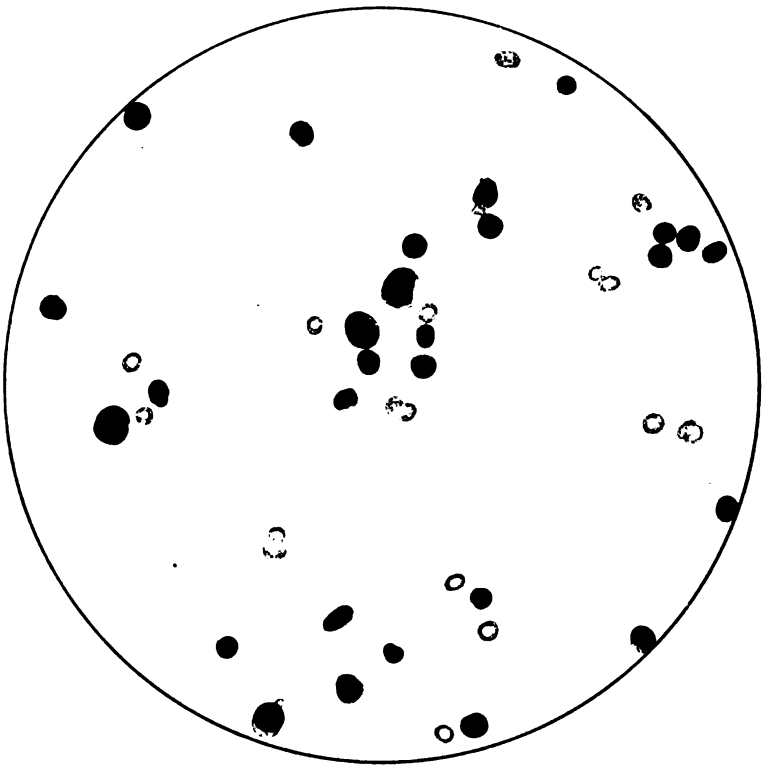


Fig. 1.

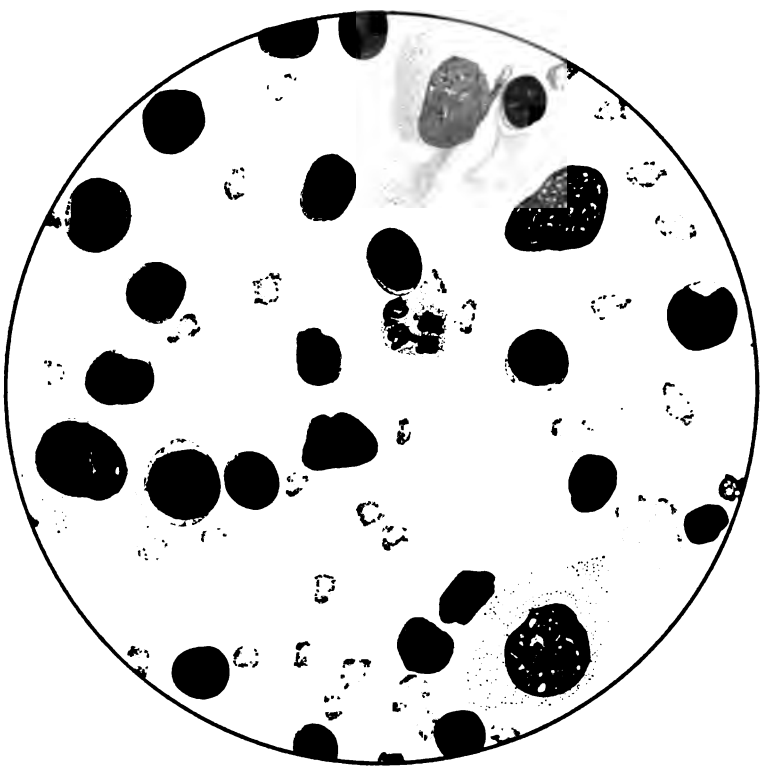


Fig. 2.

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I have referred to this question here, as it is in counting films from the peritoneal fluid of guinea-pigs that difficulty most frequently arises. The particular variety of small round endothelial cell mentioned by these authors is not very numerous, and under high powers the characteristic nucleus prevents mistakes.[1] The painting made from Case 6 with 82·2 per cent. of small lymphocytes leaves no room for doubt as to the identity of these cells, which possess nothing in common with the small round endothelioid elements. It is beyond question that small lymphocytes occur under physiological conditions in the belly fluid from guinea-pigs, and that in tuberculous infection of the peritoneal cavity the number of these cells is greatly increased.

In Table II examples 11, 13, and 37 may be regarded as showing a normal state of the peritoneal fluid, and it will be seen that, even when most numerous, the lymphocytes only amounted to 21·6 per cent.

Cases 10 and 31 (No. 2) are of special interest, for at first sight they appear to be directly at variance with what has already been said regarding the occurrence of lymphocytosis in tuberculous infection. I think they may be explained on the view that the disease had not yet gained a firm hold on the animals owing to the introduction of so few bacilli. In the one case the only evidence of infection was the finding of tubercle bacilli in a smear from the retroperitoneal glands, while in the other bacilli were again found in the same situation, and in addition the microscope revealed early changes in the spleen, with a few giant-cells. It is hardly doubtful that the infection must be making fair headway before a lymphocytosis is produced.

In the four remaining animals with well-marked macroscopic tuberculosis the percentage of small lymphocytes varied between 42·8 and 82·2. Such large numbers of these cells as are found in pleural effusions do not regularly occur in the tuberculous peritoneal exudate of animals.

Case 17 is difficult to place and I shall deal with it here. A clinical diagnosis of tuberculous mediastinitis was made; the differential count was unsatisfactory owing to degeneration of

[1] It is only fair to add that Dudgeon and Ross have noted a quite insignificant number of cells which cause a real doubt as to their classification; most probably such cells were lymphocytes.

some of the cells. The lymphocytes, however, were in good condition and only totalled 29·2 per cent. As so little fluid was obtained no inoculation experiment was possible, and nothing can be said except that the cytology of the fluid does not point to tuberculosis. But here, again, it must be remembered that Widal in one case had a somewhat similar result, and yet there were signs of an apical lesion.

Certain authors hold that in the early stages of "primary idiopathic pleurisy" the finely granular polymorphonuclear cell precedes the lymphocyte. Widal states that 10 per cent. of polynuclears may then be present. This observer also injected a culture of tubercle bacilli from man beneath the meninges of a dog. In the first count, taken on the eighth day, the proportion of polynuclears to lymphocytes was 40 to 60, but this ratio became 28 to 72 in a second count four days later. In my cases this preliminary stage with evidence of polymorphonuclears in considerable numbers was not seen, but in most instances only one examination was made.

I have little or no experience of the cytology of the cerebro-spinal fluid in disease of the nervous system apart from tuberculous meningitis, yet some reference must be made to this important branch of the subject. The only example of the kind in which I examined the cerebro-spinal fluid was one of epilepsy, where it was at first thought that a brain-tumour existed. As was to be expected, no cells were seen.

Widal, Sicard, Ravaut, Jamet, Nageotte, Babinski, and in this country Mott, may all be mentioned as having contributed to our knowledge of the subject.

Here, as elsewhere, discrepancies and difficulties occur, but writers appear to agree that lymphocytosis is present in organic disease and absent in functional disturbance of the nervous system. Thus lymphocytes are found in cerebro-spinal fluid in tabes, general paralysis of the insane, syphilitic meningo-encephalitis, and disseminated sclerosis, but are absent in epilepsy, hysteria, dementia, and cerebral neoplasm.

Many believe that in this field cytodiagnosis will find its most valued application; in the majority of cases of tabes or general paralysis, however, the clinical features prove sufficient for diagnosis without an appeal to the cytology of the cerebro-spinal fluid. On the other hand, this additional aid should be valuable

in cases of organic disease with superadded hysterical manifestations, as often occurs in women, or when the diagnosis lies between disseminated sclerosis and hysteria.

Instances are also given in the literature where an examination of the cerebro-spinal fluid has helped to establish a diagnosis in obscure cases of tabes and general paralysis.

M. J. Abadie, writing on the cytology of the cerebro-spinal fluid, gives much weight to the following statement in his conclusions: "These results go to confirm the rule, long ago laid down, that a leucocytosis in the cerebro-spinal fluid indicates an organic change in the meninges. To go farther, these variations of the leucocytes and the different cytological formulæ do not 'translate' the nature of the meningeal irritation. They cannot serve to affirm the presence of this or that particular disease: they are simply an index of the acuity, sub-acuity, or chronicity of the morbid process, as Widal has shown in his earlier researches." In their original paper dealing with pleural effusions Widal and Ravaut drew attention to this hypothesis and Abadie is arguing in confirmation of it.

It is not my purpose to question the truth of this dictum; I only hope to show that clinically it will be advantageous to allow rather more freedom in its interpretation.

We have abundant evidence that the small lymphocyte points to chronicity in the course of disease from the findings in tuberculosis, tabes (and other diffuse syphilitic infections), and also in the fact that lymphocytes are present in the cerebro-spinal fluid of sleeping sickness.

Yet syphilis of the lungs or pleuræ is so rare as to be almost a pathological curiosity, which is by no means the case with pulmonary tuberculosis or primary pleurisy complicated by effusion. Instances of specific meningitis in children suffering from congenital syphilis of course occur, but not at all commonly, and in "post-basic" examples the finely granular polymorphonuclear is found. It is a fair inference, when the lymphocyte predominates in a pleural exudate or in the cerebro-spinal fluid of a child, *that its presence is almost invariably due to tuberculosis.* It is easy to realise that difficulties occur in the case of an adult, for here the diagnosis might be between tuberculous and diffuse syphilitic infection of the meninges. Although in both conditions the lymphocyte should be the prinicipal cell of

the cerebro-spinal fluid, most probably the clinical features of the case would enable a correct diagnosis to be made.

As far as I know Nageotte is the only author who has raised this question, and in his paper he merely makes a passing reference to it.

To say that the lymphocyte merely serves as a pointer to chronic disease is, although quite true, greatly to curtail the practical utility of cytodiagnosis.

That the conclusions of Widal and Ravaut have found such universal acceptance, not only in France, but in other countries also, speaks well for the care with which they have conducted their research.

Armand-Delille and Camus questioned the value of cyto-diagnosis on the ground that they had only been able to find lymphocytes in four cases of tabes out of thirteen.

In reply, Widal and his associates showed that these observers had not been sufficiently careful in technique, and a fresh series of experiments was undertaken to demonstrate this point.

It is strange that Marcou Mutzner should have attempted to discredit the results of all previous writers on the strength of a single instance of tuberculous meningitis in which he found polynuclear cells almost exclusively. His case appears to have been one of acute miliary infection with a primary focus in the lungs, and the meningitis ran a rapid course. At autopsy, although miliary tubercles were obvious along the course of the Sylvian vessels, "a purulent muff, more than one cm. thick, was found beneath the chiasma, the bulb, and the pons"; since cultures were not taken at the *post mortem* the possibility of a mixed infection is not excluded.

I have been so fortunate as to obtain from Mr. L. S. Dudgeon the following account of a recent case. In this particular instance the cerebro-spinal fluid contained an excess of finely granular polymorphonuclear cells, but autopsy revealed the presence of tuberculosis. Previous to death, however, the *Staphylococcus albus* was obtained in pure culture from the meninges, and comment is needless.

Warthin, one of the pioneers in cytological investigation, in 1896 was working out a case of sarcoma originating in the pleural cavity. During this research he examined the exudate from one case of tuberculosis, and found endothelial cells and

fibroblasts present. He obtained the fluid from the dead-house, and his mistake is easily accounted for, as after death large flakes of endothelium would easily be detached, and in these old-standing cases only a few lymphocytes are present.

Certain discrepancies have already been referred to, and doubtless the following table of anomalies might be amplified.

TABLE III.

| Nature of disease. | Lymphocytosis.* | Author. |
|---|---|---|
| Tertiary syphilitic ulceration of soft palate. No nervous symptoms | + (3 cases) | Widal, Sicard, and Ravaut. |
| Severe secondary syphilis with persistent headache | + (2 cases) | „ |
| Sciatica | + (certain cases) | „ |
| Herpes zoster | + (some cases) | „ |
| Epidemic parotitis. The virus is supposed to have a predilection for the meninges | + (43 per cent.) | Monod, quoted by Widal. |
| Uræmia with convulsions | + (1 case) | Nieder and Mamlock. |
| Tetanus | + (2 cases); one also showed numbers of finely granular polynuclears | „ |

* In the cerebro-spinal fluid.

Although meningeal irritation has been assumed as the cause of lymphocytosis, Nieder and Mamlock urge that it is not the only factor of importance, and believe that intoxication plays an important part. They consider the positive results in syphilis, tetanus, and uræmia are to be explained on this hypothesis.[1]

Dudgeon and Ross have recently shown that those micro-organisms and toxins chiefly concerned in the bacteriology of peritonitis very frequently produce a lymphocytosis in the peritoneal exudate up to and including the first two hours after infection, and in the bone-marrow the non-granular mononuclear was the principal cell under similar circumstances.

Nieder and Mamlock think it possible that a constant mechanical irritation may produce a lymphocytosis, for they found this condition in the cerebro-spinal fluid of two rabbits after previously introducing small air-balloons beneath the skull to simulate the presence of tumours.

[1] Lovell Gulland also supports the same view.

CASE 2.—E. K—, female, aged 22 years. No family history of tuberculosis was obtained. The patient stated that she had had rheumatic fever three times.

*Present illness.*—The onset was sudden. Duration twelve days.

Physical examination revealed a right-sided pleural effusion. The apices of the lungs were healthy; a mitral regurgitant lesion was present.

Aspiration was performed and 2½ oz. of turbid yellow fluid (specific gravity 1016) were withdrawn from the right pleural sac.

*Progress of the case.*—The patient continued to improve, and when she went away the abnormal physical signs had almost cleared up.

*Temperature-chart.*—For the first few days after aspiration the temperature ranged between 103° and 101° F., with an evening rise; after this it steadily fell to normal.

*Report by patient.*—Eleven months later the patient's condition was very satisfactory.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the temperature was 102·6° F.

*Differential count of* 500 *cells*:

| | | Per cent. |
|---|---|---|
| Finely granular polymorphonuclear cells | 62 | 12·4 |
| Small lymphocytes | 249 | 49·8 |
| Large lymphocytes | 25 | 5·0 |
| Finely basophilic lymphocytes | 2 | 0·4 |
| Endothelial cells | 162 | 32·4 |
| | 500 | 100·0 |

Many of the endothelial cells showed mitotic figures.

CASE 4.—G. C—, male, aged 12 years. No family history of tuberculosis was obtained.

*Present illness.*—The patient complained of pain in the right side of a fortnight's duration.

On physical examination a large effusion into the right pleural sac was found.

On aspiration only 12 oz. of a somewhat turbid, straw-coloured fluid were obtained.

*Progress of case.*—The signs at the right base cleared up

slowly and incompletely. No sputum was obtained. On discharge the patient's condition was much improved.

*Temperature-chart.*—For the first fourteen days after aspiration the temperature rose in the evening to 103° or 102° F. and fell in the morning to about 100° F. The patient continued under observation for thirty-nine days more, when the temperature was seldom above the normal.

*Report on the patient.*—The father reported ten months later that the child was well.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the temperature was 100·3° F.

*Differential count of* 300 *cells:*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 293 | 97·6 |
| Large lymphocytes | 7 | 2·3 |
| | 300 | 100·0 |

*Inoculation experiment.*—Ten c.c. of the fluid obtained were inoculated intra-peritoneally into a guinea-pig, which was killed and examined after forty-six days.

(*a*) *Film from the peritoneal fluid.*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 268 | 53·6 |
| Endothelial cells | 228 | 45·6 |
| Finely granular polynuclear cells | 4 | 0·8 |
| | 500 | 100·0 |

(*b*) *Post-mortem examination.*—Macroscopically although a systematic examination was made of both the abdominal and thoracic viscera, the spleen alone appeared suspicious on section. A microscopical examination of this organ and of certain of the retro-peritoneal lymphatic glands revealed tuberculous foci which were passing on to caseation. No bacilli were found in smears from the glands. The above-mentioned foci were far more numerous than the naked-eye examination would have led one to suppose.

Case 5.—C. A—, female, aged 6 years. No family history of tuberculosis was obtained.

*Present illness.*—Headache had been present for six months and signs of meningeal irritation for eight days. The ears were normal.

On physical examination the pupils reacted normally, there was no involvement of the cranial nerves and no head-retraction. Rigidity of the limbs was present without paresis, and Kernig's sign was well marked. The knee-jerks were got with difficulty, patella- and ankle-clonus were absent. There was no optic neuritis and choroidal tubercles were not present.

When lumbar puncture was performed the patient's temperature was 99·6° F.; 18 drm. of cerebro-spinal fluid were obtained.

*Progress of case.*—Three more lumbar punctures were subsequently done. The patient died ten days after admission.

*Pathological aspect of the case. Differential count of* 130 *cells from the cerebro-spinal fluid:*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | .121 | 93·0 |
| Large lymphocytes | 3 | 2·3 |
| Endothelial cells | 3 | 2·3 |
| Degenerated cells | 3 | 2·3 |
| | 130 | 100·0 |

The cells were very scarce. Tubercle bacilli were not found.

*Post-mortem examination.*—The subdural space contained fluid. Tubercles were fairly numerous on the meninges and especially in the region of the chiasma; they also extended along the middle cerebral arteries. The lateral ventricles of the brain were distended and tubercles were present on the ependyma. There was a caseous gland at the bifurcation of the trachea and recent miliary tuberculosis of the lungs and pleura.

Case 6.—O. K—, male, aged 16 years. A maternal cousin died of tuberculosis.

*Present illness.*—Thirteen days before admission there was a sudden onset of pain in the left side on respiration associated with cough.

Physical examination revealed a large left-sided pleural effusion.

Aspiration was at once performed; 2½ pints of clear, straw-coloured fluid were withdrawn.

*Progress of case.*—At first the abnormal physical signs cleared up rapidly, but when the patient was discharged signs of thickened pleura persisted.

*Temperature-chart.*—For a week after aspiration the temperature gradually fell from 102° F. to nearly normal. The patient was under observation for a further period of twenty-six days, when there was only an occasional evening rise to 99° F.

*Report by patient.*—Ten months later he stated that he was much better, but still suffered from a slight cough.

*Pathological aspect of the case.*—There was no report of an examination of the sputum.

*Pleural effusion.*—At the time of aspiration the temperature was 102° F.

*Differential count of* 500 *cells.*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 462 | 92·4 |
| Large lymphocytes | 21 | 4·2 |
| Degenerated cells | 7 | 1·4 |
| Finely granular polymorphonuclear cells | 4 | 0·8 |
| Large hyaline cells | 2 | 0·4 |
| Endothelial cells | 4 | 0·8 |
| | 500 | 100·0 |

The cells were very scarce.

*Inoculation experiment.*—Eighteen c.c. of the fluid obtained from the pleural sac were injected into a guinea-pig's peritoneal cavity. The animal was killed after forty-four days.

(*a*) *Film from the pleural sac.*

| | | Per cent. |
|---|---|---|
| Finely granular polymorphonuclear cells | 5 | 1·0 |
| Small lymphocytes | 414 | 82·8 |
| Large hyaline | 23 | 4·6 |
| Coarsely granular eosinophile cells | 1 | 0·2 |
| Endothelial cells | 57 | 11·4 |
| | 500 | 100·0 |

(*b*) *Post-mortem examination.*—The animal showed massive tuberculosis in many of the viscera. The lungs and bronchial glands were involved, while the liver presented scattered foci throughout its substance. The great omentum was covered with miliary tubercles and the spleen showed large caseous areas. The retroperitoneal and lumbar glands were breaking down and circumscribed tuberculous deposits were seen on the pleural surface of the diaphragm. Histologically the glands

showed typical caseous tubercles and a few giant cells were present. Similar softening areas were seen in sections of the spleen, and infiltration by epithelioid cells was very marked. Some giant cells were also found.

CASE 8.—E. G—, female, aged 39 years. No history of tuberculosis was obtained.

*Present illness.*—Three weeks previous to admission she had a sudden onset of pain in the left side, worse on inspiration and associated with cough.

On examination signs of a left-sided pleural effusion were found. There were signs of phthisis at the left apex and tubercle bacilli were present in the sputum.

*Progress of case.*—The patient improved steadily up to the time she was discharged, but friction sounds were audible for three weeks after aspiration.

*Temperature-chart.*—During the entire course of the illness there was no notable pyrexia.

*Report by the patient.*—Ten months later it was stated that a bad cough was present, associated with cardiac pain.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the temperature was 98·8° F. Two and a quarter pints of clear straw-coloured fluid were obtained. It contained a heavy trace of albumen.

*Differential count of* 500 *cells.*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 416 | 83·2 |
| Finely granular polynuclear cells | 6 | 1·2 |
| Large lymphocytes | 20 | 4·0 |
| Degenerated cells | 14 | 2·8 |
| Endothelial cells | 44 | 8·8 |
| | 500 | 100·0 |

The cells were fairly abundant. Tubercle bacilli were present in the sputum.

CASE 10.—E. S—, male, aged 37 years. No family history of tuberculosis was obtained.

*Present illness.*—The patient had previously suffered from bronchitis and pleurisy. He "had brought up a pint of bright

red blood." At the onset of the present illness there was no pain.

On physical examination signs of a moderate amount of effusion into the pleural sac were found. On aspiration, however, 4 pints 6 oz. of fluid were withdrawn.

*Progress of case.*—On discharge the patient had greatly improved, but the abnormal signs had not quite cleared up and some friction was still audible.

*The temperature-chart.*—At first the morning temperature was 99° and the evening 101·2° F. Although during observation the temperature fell to a certain extent, this type of pyrexia was present during the course of the case.

*Report by patient.*—Ten months later slight shortness of breath on exertion was the only symptom.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the patient's temperature was 99·4° F.; 4 pints 6 oz. of dirty yellow, blood-stained fluid were withdrawn. It did not appear purulent, and in small quantities was comparatively clear. It contained a heavy trace of albumen.

*Differential count of* 500 *cells.*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 475 | 95·0 |
| Large lymphocytes | 22 | 4·4 |
| Large hyaline cells | 2 | 0·4 |
| Degenerated cells | 1 | 0·2 |
| | 500 | 100·0 |

*Inoculation experiment.*—Twelve c.c. of the above fluid were injected intra-peritoneally into a guinea-pig; the animal was killed and examined after forty-seven days.

(*a*) *Film preparation from the peritoneal fluid.*

| | | Per cent. |
|---|---|---|
| Endothelial cells | 489 | 97·8 |
| Small lymphocytes | 8 | 1·6 |
| Coarsely granular polynuclear cells | 3 | 0·6 |
| | 500 | 100·0 |

Numerous bacilli, cocci, and diplococci were present in the film; these organisms were probably of no significance.

*Post-mortem examination.*—Macroscopically all the thoracic and abdominal viscera appeared to be normal. Mediastinal and retroperitoneal glands were taken for further examination.

Histologically the spleen showed marked cellular proliferation in the walls of the smaller blood-vessels, and the lymphoid cells were largely replaced by the epithelioid variety. Numerous scattered particles of pigment were seen which did not lie within the cells. On making a smear from the retroperitoneal lymphatic glands seven undoubted tubercle bacilli were found.

Case 11.—G. B—, male, aged 36 years. No family history of tuberculosis was obtained.

*Present illness.*—The patient had had two previous attacks of right-sided pneumonia. The present attack had a sudden onset associated with pain in the left side and shortness of breath. On physical examination a left-sided pleural effusion was found. Aspiration was performed and three pints of fluid withdrawn.

*Progress of the case.*—After an illness of six weeks' duration the patient improved sufficiently to go out, but abnormal physical signs in the chest persisted.

*Temperature-chart.*—For the first eleven days after aspiration there was an evening rise of temperature to 102° F. and a morning fall to 100° F., after which only slightly marked pyrexia was observed.

*Report by the patient.*—Ten months later there were no abnormal signs in the lungs.

*Pathological aspect of the case; pleural effusion.*—At the time of aspiration the temperature was 100·2° F. A culture from the fluid was taken into broth; it proved to be sterile. Three pints of clear, light brown fluid were withdrawn, which contained a moderate trace of albumen.

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 3 | 0·6 |
| Small lymphocytes | 445 | 89·0 |
| Large lymphocytes | 38 | 7·6 |
| Large hyaline | 5 | 1·0 |
| Coarsely granular polynuclear cells | 1 | 0·2 |
| Endothelial cells | 8 | 1·6 |
| | 500 | 100·0 |

*Inoculation experiment.*—Twenty c.c. of the fluid were inoculated intra-peritoneally into a guinea-pig, which was killed after forty-six days.

| (*a*) *Film from peritoneal exudate.* | | Per cent. |
|---|---|---|
| Endothelial cells | 243 | 97·2 |
| Small lymphocytes | 7 | 2·8 |
| *Film from the pleural sac.* | 250 | 100·0 |
| Finely granular polynuclear cells | 2 | 0·4 |
| Small lymphocytes | 97 | 19·4 |
| Large hyaline | 17 | 3·4 |
| Coarsely granular polynuclear cells | 3 | 0·6 |
| Endothelial cells | 381 | 76·2 |
| | 500 | 100·0 |

(*b*) *Post-mortem examination.* — There was no macroscopic evidence of tuberculosis in any of the glands, spleen, or great omentum. Histologically the spleen was quite normal, and smears from both the mediastinal and the retroperitoneal glands showed no bacilli.

Case 12.—C. J—, female, aged 22 years. No family history of tuberculosis was obtained.

*Present illness.*—For one month before admission the patient suffered from a "hacking cough." The onset was sudden, with right-sided pain and shortness of breath.

On examination there were physical signs of a right-sided pleural effusion. Aspiration was performed and 1 pint 2 oz. of fluid withdrawn.

*Progress of case.*—The abnormal signs almost entirely cleared up before the patient was discharged.

*Temperature-chart.*—There was only slight pyrexia at any time during the period the patient was under observation.

*Report by patient.*—Ten months later the general condition was very good.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the temperature was normal; 1 pint 2 oz. of straw-coloured fluid were obtained.

| *Differential count of* 500 *cells.* | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 1 | 0·2 |
| Small lymphocytes | 454 | 90·8 |
| Large lymphocytes | 18 | 3·6 |
| Large hyaline cells | 3 | 0·6 |
| Endothelial cells | 24 | 4·8 |
| | 500 | 100·0 |

No tubercle bacilli were found in the sputum.

Case 13.—E. S—, female, aged 16 years. The patient's father and a maternal uncle both died of phthisis.

*Present illness.*—Since childhood she suffered with chronic cough and attacks of pain in the left side. Two months before admission there was an attack of influenza. The left-sided pain was worse than usual after this and had been increasing for ten days before the patient entered the hospital.

There were physical signs of an effusion into the left pleural sac. Aspiration was performed and 1 pint 2 oz. withdrawn.

*Progress of the case.*—Convalescence was uninterrupted.

*Temperature-chart.*—For five days after aspiration the morning temperature was 97° and the evening 100·5° F. Subsequently there was no pyrexia.

*Report by the patient.*—Ten months later the patient still suffered from her chest and the cough was very troublesome.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the patient's temperature was 99° F.; 1 pint 2 oz. of pale yellow fluid were withdrawn

| *Differential count of* 500 *cells.* | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 5 | 1·0 |
| Small lymphocytes | 428 | 85·6 |
| Large lymphocytes | 30 | 6·0 |
| Endothelial cells | 30 | 6·0 |
| Degenerated cells | 7 | 1·4 |
| | 500 | 100·0 |

No sputum was available for examination.

*Inoculation experiment.*—Eight c.c. of the fluid were inoculated intra-peritoneally into a guinea-pig. The animal died in eighteen hours.

| (*a*) *Films from the peritoneal exudate.* | | Per cent. |
|---|---|---|
| Small lymphocytes | 108 | 21·6 |
| Large lymphocytes | 12 | 2·4 |
| Endothelial cells | 375 | 75·0 |
| Degenerated cells | 5 | 1·0 |
| | 500 | 100·0 |

One film stained by Gram showed no micro-organisms,

(*b*) *Post-mortem examination.*—On examination a quantity of unabsorbed fluid was found in the peritoneal cavity. There was no evidence of peritonitis. All the thoracic and abdominal viscera appeared normal. Histologically there was no evidence of disease in the spleen, liver, kidneys, or lungs. Smears from the retro-peritoneal and mediastinal lymphatic glands were negative.

Case 17.—V. J—, female, aged 5 years. No family history of tuberculosis was obtained.

*The present illness.*—Four days before admission cough and pain in the right side were complained of. Two days later the physical signs of broncho-pneumonia developed over the right upper lobe. As these signs persisted for ten days after admission an empyema was suspected. Aspiration was performed and a small quantity of quite clear serous fluid withdrawn.

*Progress of the case.*—The patient continued under observation for a further period of eight weeks. The general health gradually improved; the signs at the right apex had not completely cleared up when the child was discharged. The following X-ray report was obtained: "The appearances did not suggest neoplasm as the shadow was not definite enough. It appeared as if there was consolidation of the front of the right lung." A diagnosis of tubercular mediastinitis was made. On admission the weight was 2 st. 2 lb., and on discharge 2 st. 5 lb. 8 oz.

*The temperature-chart.*—For the first month the temperature was markedly hectic with an evening rise. The readings varied between 97° and 103° F. The range of the pyrexia gradually subsided and for the last six weeks the curve rarely rose above the normal.

*Pathological aspect of the case.*—Only a few ounces of clear fluid were obtained; just previous to the time of aspiration the temperature was 101° F.

| *Differential count of* 500 *cells:* | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 52 | 10·4 |
| Mononuclear neutrophil cells | 275 | 55·0 |
| Large lymphocytes | 13 | 2·6 |
| Large hyaline cells | 1 | 0·2 |
| Small lymphocytes | 134 | 26·8 |
| Degenerated cells | 25 | 5·0 |
| | 500 | 100·0 |

It was impossible to classify the mononuclear neutrophils. All cells except the lymphocytes were greatly degenerated. No micro-organisms were seen on the films. The blood was examined twice, but no great departure from the normal was detected.

Case 18.—T. M—, male, aged 29 years. One sister died of tuberculous peritonitis.

*Present illness.*—The patient was found to be suffering from a right-sided hydrocele of the tunica vaginalis. There was a history of insidious onset for eight months. After tapping definite thickening of the epididymis was found. There was slight pain. The patient had been previously tapped three times in six months.

A diagnosis of tubercular testicle was made and an operation performed in which small localised foci were removed from the epididymis.

*Pathological aspect of the case. Hydrocele fluid.*

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 10 | 2·0 |
| Small lymphocytes | 256 | 51·2 |
| Large hyaline | 8 | 1·6 |
| Endothelial cells | 226 | 45·2 |
| | 500 | 100·0 |

Films stained for tubercle bacilli gave a negative result.

No spermatozoa were seen.

Case 19.—A. W—, male, aged 12 years. No family history of tuberculosis was obtained.

*Present illness.*—There was a sudden onset of paralysis, starting on the left side of the body. From the hand the paralysis spread to the arm and finally became hemiplegic in distribution. Immediately after the loss of power it appears that he had a fit in which he lost consciousness.

On admission the temperature was 103·4° F. and the pulse 160.

On examination a few fine crepitations were audible in the right axilla. The thighs and knees were flexed; the arms were flexed at the elbows, the hands forcibly supinated, and the fingers extended. The pupils were inactive to light; the optic discs were

normal; there was neither nystagmus nor strabismus. The cranial nerves were normal. The knee-jerks were very variable, the plantar reflex was of the extensor type, and there was a tendency to ankle-clonus. Kernig's sign was present.

*Progress of the case.*—Two lumbar punctures were performed, and a provisional diagnosis of tubercular meningitis was made. As time went on it became apparent that the patient was suffering from epilepsy, and all the abnormal physical signs disappeared. He was, when discharged, very much better.

*The temperature-chart.*—The curve descended sharply from 103·4° F. on admission to the normal after three and a half days, and during the remainder of the period the patient was observed the temperature was normal.

*Report by the patient.*—Nine months later the father stated that the patient had made a complete recovery.

*Pathological aspect of the case.*—Cerebro-spinal fluid. (When lumbar puncture was performed the patient's temperature was 101·6° F.) Three films were examined for cells with a negative result. No micro-organisms were seen. Cultures taken from the fluid proved sterile.

CASE 27.—R. H—, female, aged 7 months. The father had had pleurisy and two cousins died of meningitis.

*The present illness.*—Onset one month before admission with irritability, fixed stare, and wasting. There was vomiting associated with drowsiness and stiffness of the neck-muscles.

On examination there was marked head-retraction and stiffness of the neck. A twitching of the facial muscles and of the arms was noted. The cranial nerves were normal. The pupils were moderately dilated and reacted to light. The optic discs were normal. The knee-jerks were very brisk, but there was no ankle-clonus. The anterior fontanelle was bulging.

*Progress of case.*—The patient became steadily worse and died in a comatose state five weeks after admission.

*Temperature-chart.*—Till a few days before death the record was of the inverse type; in the morning the temperature was between 99·5° and 101° F., while in the evening a fall to 97° F. occurred.

*Pathological aspect of the case.*—On performing lumbar puncture 2 drms. of cerebro-spinal fluid were obtained. The temperature at the time of operation was 100·4° F.

*Differential count of* 100 *cells:*

| | |
|---|---|
| Finely granular polynuclear cells | 2 |
| Small lymphocytes | 77 |
| Large lymphocytes | 2 |
| Endothelial cells | 3 |
| Degenerated cells | 16 |
| | 100 |

The cells were very scanty. The degenerated ones were most probably finely granular polynuclear cells.

*Post-mortem report.*—Tubercles were thickly scattered on the upper and under surface of the cerebellum and in the fissure of Sylvius; they were also very numerous in the choroid plexus and on the ependyma of the lateral ventricles. The membranes of the spinal cord were also involved in the tubercular process, and caseous cervical lymph-glands were found. The cerebro-spinal fluid was in excess. Caseating foci were present in the mediastinal glands and to a slight extent in the lungs. There were two tuberculous ulcers in the ileum, and three of the mesenteric glands were breaking down.

Case 29.—A. O—, male, aged 46 years. No family history of tuberculosis was obtained.

*The present illness.*—The patient had been ill for one month, with cough and subsequently pain in the left side.

On physical examination a large, left-sided pleural effusion was detected. On aspiration 36 oz. of fluid were withdrawn. There were some sharp crepitations at the left apex.

*Progress of the case.*—The patient continued under observation for ten weeks. His weight increased, but the abnormal physical signs had not quite cleared up on discharge.

*The temperature-chart.* — This was strongly suggestive of tuberculosis.

*Report by the patient.*—Seven months later he stated that pain and cough were still present, but he was able to resume work.

*Pathological aspect of the case.* — At the time of aspiration the temperature was 100·8°. There were 36 oz. of pale, straw-coloured fluid, specific gravity 1020, reaction alkaline; when the boiling test was applied solidification occurred.

*Differential count of* 100 *cells:*

| | |
|---|---|
| Finely granular polynuclear cells | 2 |
| Small lymphocytes | 87 |
| Endothelial cells | 9 |
| Degenerated cells | 2 |
| | 100 |

Tubercle bacilli were found in the sputum.

*Inoculation experiment.*—Ten c.c. of the fluid were injected intra-peritoneally into a guinea-pig. The animal was killed after forty-four days.

*Film from the peritoneal fluid:*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 214 | 42·8 |
| Large lymphocytes | 12 | 2·4 |
| Endothelial cells | 263 | 52·6 |
| Finely granular polynuclear cells | 11 | 2·2 |
| | 500 | 100·0 |

*Post-mortem examination.*—Tubercles were present on naked-eye examination in the liver, spleen, and retroperitoneal glands. The kidneys were apparently normal. There was no fluid in the pleural sacs and the lungs appeared healthy. Histologically typical tubercles were found in the liver, spleen, and retro-peritoneal glands, and a fair number of giant cells were seen. The kidneys showed early changes, but the lungs were normal.

Case 30.—F. S—, male, aged 8 years. No family history of tuberculosis was obtained. A month previous to admission received a kick in the right side, and has had pain since.

On physical examination signs of a right-sided pleural effusion were found. On aspiration only 4 oz. of serous fluid were obtained.

*Progress of case.*—On discharge there was still dulness over the right lower lobe, and an occasional friction rub.

*The temperature-chart.*—On admission the temperature was 101·4° F., and up to the time of aspiration it varied between 103° and 104° F. (evening rise.) After aspiration the chart recorded a normal temperature,

*Report from patient.*—Seven months later it was reported that the patient continued to have attacks of pain in the right side.

*Pathological aspect of the case.*—At the time of aspiration the temperature was 100·8° F.; 4 oz. of straw-coloured fluid were obtained.

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 368 | 73·6 |
| Large lymphocytes | 21 | 4·2 |
| Endothelial cells | 22 | 4·4 |
| Finely granular polynuclear cells | 89 | 17·8 |
| | 500 | 100·0 |

Case 31.—J. V—, male, aged 20 years. The father was said to have died from "chest trouble."

*The present illness.*—For three weeks there had been cough and for thirteen days dyspnœa, accompanied by pain in the left scapular region. On physical examination a large left-sided pleural effusion was found. Aspiration was performed.

*Progress of case.*—The abnormal physical signs were well marked when the patient was discharged, but he had gained in weight.

*The temperature-chart.* — Immediately after aspiration the temperature varied between 101° and 104° F. for four days. The patient continued under observation for nine weeks, during the latter six of which the temperature rose on the average to 100° F. in the evening.

*Pathological aspect of the case.*—At the time of aspiration the temperature was 101·3° F.; 95 oz. of clear fluid were obtained; reaction alkaline; on applying the boiling test solidification occurred. *No cells* were seen in film preparations of the fluid. Five slides were examined. No tubercle bacilli were found in the sputum.

*Inoculation experiment.* — Two guinea-pigs were inoculated intra-peritoneally with the fluid. The animals were killed eight weeks later.

*Guinea-pig I.—Autopsy.*

*Film from the peritoneal fluid.*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 4 | 0·8 |
| Small lymphocytes | 404 | 80·8 |
| Large lymphocytes | 28 | 5·6 |
| Coarsely granular polynuclear cells | 1 | 0·2 |
| Endothelial cells | 63 | 12·6 |
| | 500 | 100·0 |

Macroscopically the spleen, liver, intestines, and mesentery were tuberculous. The great omentum was involved and there were scattered tubercles on the parietal peritoneum. The iliac, retroperitoneal, anterior and posterior mediastinal glands were caseous. The lungs and kidneys appeared to be normal. Tubercle bacilli were found in smears made from the retroperitoneal glands. Microscopically the spleen showed typical caseous tubercles scattered throughout its substance. In other parts numerous giant cells were present, with alterations in the surrounding tissue showing the earlier stages of the process.

*Guinea-pig II.—Autopsy.*

*Film from the peritoneal fluid.*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 4 | 0·8 |
| Small lymphocytes | 15 | 3·0 |
| Large lymphocytes | 1 | 0·2 |
| Endothelial cells | 479 | 95·8 |
| Coarsely granular polynuclear cells | 1 | 0·2 |
| | 500 | 100·0 |

No naked-eye evidence of tuberculosis was seen in any of the organs, glands, mesenteries, or peritoneum. Tubercle bacilli were found in smears made from the retroperitoneal glands. Sections of the spleen examined microscopically showed cell-proliferation in the neighbourhood of the blood-vessels and isolated giant cells in small groups of two or three were found

with epithelioid cell proliferation surrounding them and replacing the normal lymphoid tissue.

Case 34.—G. A—, male, aged 11 years. No family history of tuberculosis was obtained.

*The present illness.*—For five weeks previous to admission there had been pain in the right side of the chest, which gradually increased in severity. On examination a small collection of fluid was found at the right base and aspiration was performed.

*Progress of case.*—The patient was kept under observation for five weeks. He was finally discharged completely convalescent.

*The temperature chart.*—For a fortnight the temperature ranged between the normal and 102° F. (evening). For the remainder of the time there was no pyrexia.

*Report by the patient.*—No further information could be obtained.

*Pathological aspect of the case.*—At the time of aspiration the temperature was 101·4° F.; 11 oz. of clear fluid were obtained.

*Differential count of* 200 *cells.*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 1 | 0·5 |
| Small lymphocytes | 177 | 88·5 |
| Large lymphocytes | 11 | 5·5 |
| Finely basophilic cells | 1 | 0·5 |
| Endothelial cells | 10 | 5·0 |
| | 200 | 100·0 |

Case 36.—H. M—, male, aged 5 years. No family history of tuberculosis was obtained.

*The present illness.*—On admission the patient complained of pain in the left side for one month, which had abated, and dyspnœa. On physical examination a massive left-sided pleural effusion was found. He was immediately aspirated; 3 pints and 18 oz. of fluid were obtained.

*Progress of case.*—The patient continued under observation for seven weeks. When discharged the base of the lung had not cleared and crepitations were audible at the left apex.

*The temperature-chart.*—An evening rise of temperature to 100° F. continued at intervals till the discharge of the patient.

*Report by patient.*—Six months later he still complained of cough, dyspnœa, and sharp pain in the left side.

*Pathological aspect of the case.*—Three pints eighteen ounces of straw-coloured fluid were withdrawn. At the time of aspiration the temperature was 100·4° F.

*Nature of cells.*—These consisted entirely of small lymphocytes. As there were only about three dozen cells on the whole film a differential count was not done.

*Sputum.*—Two examinations for tubercle bacilli were negative.

*Inoculation experiment.*—Fourteen c.c. of the above fluid were inoculated intra-peritoneally into a guinea-pig, and the animal was killed after ten weeks.

*Film from the peritoneal fluid:*

| | | Per cent. |
|---|---|---|
| Small lymphocytes . . . . | 221 | 44·2 |
| Large lymphocytes . . . . | 7 | 1·4 |
| Endothelial cells . . . . | 272 | 54·4 |
| | 500 | 100·0 |

*Post-mortem examination.*—Macroscopically the spleen and retro-peritoneal glands were tuberculous, and there were a few scattered foci in the lungs. The omentum and other organs showed no changes.

Tubercle bacilli were found in smear preparations from the retroperitoneal glands. Microscopically the lymph-glands showed a small area of normal tissue at the periphery, but beyond this the gland-substance was replaced by a widespread proliferation of epithelioid cells with numerous giant cells scattered at random therein. There were one or two small points of caseation. The cells of the blood-vessel walls were also proliferated. The lungs contained discrete tubercles showing early caseous changes and a fair number of giant cells. The spleen was obviously caseous, but owing to an error in technique could not be cut.

Case 37.—A. B—, male. Family history not obtained.

*The present illness.*—The onset was gradual and the symptoms latent till the patient experienced increased irritation from cough and progressive dyspnœa.

On physical examination a large left-sided pleural effusion was found.

No record of the temperature or of the after-history of the case could be obtained.

*Pathological aspect of the case.*—Ten c.c. of fluid were obtained in a test-tube; there was a quantity of sediment and clot at the bottom.

*Nature of cells.*—The cells consisted entirely of small lymphocytes, but there were so few on the film that a differential count was not done.

*Sputum.*—On examination numerous tubercle bacilli were found.

*Inoculation experiment.*—Nine c.c. of the above fluid were inoculated intra-peritoneally into a guinea-pig; three days later the animal died with acute symptoms.

*Film from peritoneal fluid:*

| | | Per cent. |
|---|---|---|
| Endothelial cells | 419 | 83·8 |
| Small lymphocytes | 63 | 12·6 |
| Large lymphocytes | 10 | 2·0 |
| Finely granular polynuclear cells | 8 | 1·6 |
| | 500 | 100·0 |

*Post-mortem examination.*—Macroscopically all the thoracic and abdominl viscera appeared normal. There was slight flushing of the peritoneum, but no adhesions or flakes were found. Smear preparations from the anterior mediastinal and iliac glands showed no tubercle bacilli. On microscopic examination no evidence of tuberculosis was found in the spleen or retroperitoneal lymphatic glands.

## Cytodiagnosis in Malignant Disease.

The crucial point which has to be decided here is whether or not it is possible to recognise an isolated cell as possessing malignant characteristics.

It is probable that malignant growths complicated by pleural effusion, hydrocele, or ascites can only rarely, and under exceptional circumstances be diagnosed from the cytological picture presented by these fluids.

Those cases in which considerable portions of breaking-down neoplasm occur are not at present under discussion; vesical tumour, for instance, has often been recognised from such appearances when the urine was submitted to histological examination. Lovell Gulland investigated three cases of pleurisy complicating carcinoma of the lung. He considers that many cells from the growth are often to be found in the fluid; these are swollen, larger than those usually seen, present abnormalities of the nucleus, and often show fatty degeneration. One of his cases showed a large excess of polymorphonuclear cells.

Earl has also examined effusions due to neoplasm of the serous membranes. He concludes that carcinoma-cells may be absent, but are *occasionally* undoubtedly present. The authority of Quincke is given for the statement that neoplastic cells often contain glycogen, while it is only rarely present in the endothelial variety. The same writer holds that the presence of mitotic figures is greatly in favour of malignant disease.

Barjon and Cade found that their results in carcinomatosis of the peritoneum were too variable to be of any diagnostic value. In two examples the small lymphocyte was found to be the principal cell, while in four others endothelial elements predominated.

Warthin's instance of primary sarcoma originating in the pleural sac, besides having a great historical interest, is almost unique.

In spite of the fact that a spindle-celled sarcoma involving the pleura is very uncommon, it appears to me an extremely hard matter to make a diagnosis from an examination of isolated cells, however numerous they may be in the fluid obtained, an impression which is strengthened by a perusal of this paper. Dr. Warthin did not find any large masses of aggregated cells upon an examination of which he might have based his claim that the growth was diagnosed cytologically. The presence of numerous mitotic figures is certainly in favour of neoplasm, but they may occur in non-malignant cases. The addition, too, of a table to differentiate sarcoma-cells from fibroblasts tends to show that our author felt he was grappling with a difficulty. Naturally he insists that his cytological findings were verified by autopsy, but that is not the point.

In my opinion Widal and Ravaut partly explain the cell formulæ found in malignant disease when they class these cases with the "mechanical effusions." In certain instances a fair number of polynuclear cells is seen; when this happens it indicates that some inflammatory reaction has occurred during the development of the neoplasm which, as is well known, is not uncommon. If endothelial cells predominate, the new growth is

TABLE IV.

| Nature of case. | Primary growth. | Secondary deposits. | Nature of cells. | Mitosis. |
|---|---|---|---|---|
| Sarcoma of testis, hydrocele (38) | Testis, small round cells | Spermatic cord | Endothelial cells = 86·6 per cent. | — |
| Carcinoma of liver, ascites (20) | Liver | — | Endothelial cells = 77·4 per cent. | — |
| Malignant teratoma, ascites (33) | Left ovary | Liver (one node) | Polynuclears = 41·4 per cent., endothelial cells = 21 per cent., much free blood | — |
| Carcinoma of lung, effusion (24) | Tissues round œsophagus, spheroidal cells | Right lung, pleura, liver, mediastinal and retro-peritoneal glands, etc. | Small mononuclear cells = 42·4 per cent. | — |
| Carcinomatosis of pleuræ, effusion (40) | Left ovary | Peritoneum, both pleuræ | Endothelial cells = 90·8 per cent., a film stained by van Giesen's method did not bear this out. | — |
| Sarcoma of testis, hydrocele (14) | Left testis, small round cells | Peritoneum, omentum, surface of intestines, retroperitoneal glands, liver, spleen, left kidney, pleuræ, anterior mediastinal glands | Small mononuclear cells = 77·0 per cent. | — |

merely causing a mechanical pressure effect. Table IV gives my results in six examples of malignant disease, and many of them can be explained on Widal's hypothesis. The most striking point is the entire absence of mitotic figures in the cells. In all instances special attention was directed to this factor, and the specimens carefully examined for evidence of mitosis. The only case in which a few mitotic figures were found in the endothelial cells has already been dealt with, and as the patient was in

excellent health eleven months after the attack of pleurisy, her illness could not have been due to new growth.

This failure to find any evidence of mitosis in no way invalidates its importance, and when a cytological diagnosis is possible it will probably depend on the presence of numerous mitotic figures in the cells.

In two cases (sarcoma of testis and hydrocele, carcinoma of liver and ascites) the endothelial cells varied between 77·4 and 86·6 per cent. of the total number. In these instances the most feasible explanation is that the new growth acted mechanically by pressure on the blood-vessels, and consequently endothelial cells predominated in the fluids examined. Hence the nature of the cells does not afford a clue to that of the disease, and merely indicates a pressure effect.

Case 33, malignant teratoma[1] of ovary with ascites, may also be taken as showing a fair number of endothelial cells; for, although they only amounted to 21 per cent., there was a quantity of blood present which would account for the polynuclear cells (41·4 per cent.) being more numerous than usual. In this example the lymphocytes numbered 33 per cent., and no cells pointing to malignant disease were present in the ascitic fluid.

In a case of pulmonary carcinoma (Case 24) 33 per cent. of endothelials were found, and the lymphocytes amounted to 42·4 per cent. No cells at all suggestive of neoplasm were seen.

In the second case of testicular sarcoma (14) the small round-celled elements amounted to 77 per cent., and it is possible that they might have been sarcoma cells, but no absolute proof of this was obtained. The outline of the cells was ill-defined and they stained diffusely, otherwise they were morphologically identical with the small lymphocyte. Case 38 shows that small round cells in the fluid are not constant in sarcoma of the testis when complicated by hydrocele.

Case 40 is of very special interest. Diffuse carcinomatosis of both pleuræ and of the peritoneum was found at autopsy. The primary growth proved to be carcinoma of the left ovary. A film from the pleural fluid stained by Leishman appeared to contain 90·8 per cent. of endothelial cells. Another preparation

[1] For full report see "A Case of Malignant Teratoma of Ovary," L. S. Dudgeon, 'Journal of Obstetrics and Gynæcology,' January, 1906.

stained by van Gieson and hæmalum aroused suspicion that malignant disease might be present. The cells were aggregated into placards considerably larger than those commonly seen formed by endothelial elements. From the shape and size of the cells and their nuclei neoplasm was considered to be present, and this was subsequently found to be the case.[1]

I regard the above example as the exception which goes to prove the rule. Too much has been claimed for cytological methods where neoplasm is concerned. In these instances cytodiagnosis will exclude tuberculous infection, but not some inflammatory condition complicating a new growth, for here polynuclear cells might predominate to such an extent as to lead to the conclusion that some acute infective process is present instead of malignant disease. Simple tumour or malignant neoplasm may both produce pressure effects, and then present an identical cell picture in which the endothelial predominates. The only conclusion possible is that cytodiagnosis is of very limited value in malignant disease. I regret that the glycogenic reaction was not tried in any of my cases.

Case 14.—F. B—, male, aged 16 years.

*Present illness.*—There was a history of injury previous to admission into the hospital. A hydrocele subsequently formed from which 2 oz. of blood-stained fluid were withdrawn. On examination a tumour of the left testicle and epididymis was found. The process of growth involving the cord was 2 inches in diameter below, and could be traced up into the abdomen. The testis felt hard and heavy.

At operation the neoplasm was found to be a sarcoma of the epididymis, but the testicle was also infiltrated.

*Progress of case.*—Fourteen days after operation free fluid was diagnosed in the abdomen. During the last five weeks of life paracentesis abdominis was performed four times, and on one occasion 48 fluid oz. were removed.

*Pathological aspect of the case. Report on the tumour.*—Histologically the neoplasm was a round-celled sarcoma. Vascular sarcoma-tissue was mixed with large strands of fibrous

[1] Attention is called to the peculiar green coloration of the cells. Mr. L. S. Dudgeon has observed it in cases where hæmalum and van Gieson's reagent were used to stain tissues containing blood-clot.

tissue. The growth had undergone myxomatous degeneration, but areas of normal testicular tissue were seen in some of the sections. No cartilage was seen.

*The fluid.*—This was pale-green and clear. The reaction was alkaline. Specific gravity 1014. A trace of albumen was present. Later the quantity of albumin was greatly increased, and pus was also found to be present.

*Differential count of* 500 *cells* (hydrocele fluid):

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 385 | 77·0 |
| Large lymphocytes | 25 | 5·0 |
| Endothelial cells | 90 | 18·0 |
| | 500 | 100·0 |

The small lymphocytes stained more deeply than usual, and the surrounding ring of protoplasm was not so evident as it is in most cases.

*Post-mortem report.*—On opening the abdomen 36 oz. of opaque fluid escaped. The great omentum was 1 inch thick, and studded with white growth. The intestines were covered with small nodules of growth, and the mesenteric glands were infiltrated. The retroperitoneal glands were the seat of a massive growth, which showed mucoid degeneration and hæmorrhagic changes in parts. In the liver there were secondary deposits of about the diameter of a shilling. On the surface of the spleen there were small deposits, but none were found in its substance. Both kidneys were imbedded in a mass of neoplastic tissue extending outwards from the retroperitoneal glands. The left kidney was invaded but the right was normal. The pleural cavity contained 40 oz. of fluid, and the pleuræ on both sides were studded with growth. The lungs were not invaded, but the glands in the anterior mediastinum were involved. On the left side several malignant glands of the neck were present. The right testicle was normal, as also was the brain.

Case 20.—J. S—, male, aged 50 years. The patient had been an habitual drinker of some four pints of beer *per diem*.

*Present illness.*—Three months previous to admission he experienced gnawing epigastric pain and noted a gradual increase in the size of the abdomen. On examination he was

slightly jaundiced. There were physical signs of a large quantity of free fluid in the abdominal cavity, but the liver could not be palpated (umbilical measurement, 43 in.).

*Progress of case.*—Paracentesis abdominis was twice performed. After the last operation examination of the liver proved the case to be one of carcinoma.

*Temperature-chart.*—There was no pyrexia.

*Pathological aspect of the case.*—Ten pints ten ounces of clear fluid were obtained.

*Differential count of* 500 *cells:*

| | | |
|---|---|---|
| Finely granular polynuclear cells | 4 | 0·8 |
| Mononuclear cells (small) | 108 | 21·6 |
| Endothelial cells | 387 | 77·4 |
| Coarsely granular polynuclear cells | 1 | 0·2 |
| | 500 | 100·0 |

The mononuclear cells were morphologically identical with the small lymphocytes of the blood, except that they were stained more deeply.

Case 24.—J. E—, female, aged 65 years.

*Present illness.*—For about three weeks previous to admission there had been cough, dyspnœa, and pain. She stated that she was losing weight, and a diagnosis of "? mediastinal growth" had been made. On examination a large pleural effusion was found on the right side, reaching as high as the third rib anteriorly. The pulses in the radial, carotid, and temporal arteries were equal; the right pupil was larger than the left, but its size varied from day to day. The larynx was normal. One week after admission the pleural effusion reached the second rib anteriorly, and more distress from dyspnœa was experienced. On aspiration being performed 20 oz. of clear fluid were removed from the right pleural cavity.

*Progress of case.*—Improvement was maintained for five weeks, after which time the chest rapidly refilled and dyspnœa became more urgent. At a second aspiration 25 oz. of fluid similar to the first sample were obtained. Subsequently the patient sank very rapidly, and died suddenly during an attack of dyspnœa.

*Pathological aspect of the case. Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 109 | 21·8 |
| Small mononuclear cells | 212 | 42·4 |
| Large mononuclear cells | ·5 | 1·0 |
| Coarsely granular polynuclear cells | 9 | 1·8 |
| Endothelial cells | 165 | 33·0 |
| | 500 | 100·0 |

The majority of the finely granular polynuclear cells were characterised by their small size, but the nucleus and granules were to be distinguished in every case on careful focussing. The small mononuclear cells differed from the small lymphocyte of the blood by being smaller and having the surrounding ring of protoplasm narrower. These cells stained diffusely.

*Post-mortem report.*—Twenty-five ounces of fluid were found in the right pleural cavity. About one third of the right lung was infiltrated with new growth which had spread along the bronchi chiefly into the lower lobe, which with the middle lobe was solid and airless. The right upper lobe was also infiltrated. The left upper and lower lobes were studded with nodules of growth spreading from the root of the lung. The primary growth appeared to be from the region round about the œsophagus, which was encircled by it, although there was very little stenosis and the mucous membrane was normal. Secondary growths were found on the right pleura and a nodule the size of a hazel-nut in the liver. There was also a small nodule in the left kidney. The bronchial, all the mediastinal, mesenteric, and retroperitoneal glands showed evidence of secondary infiltration, as also did especially the glands along the aorta. The pericardium was infiltrated but the cardiac valves were normal. On section the growth proved to be a spheroidal-celled carcinoma.

Case 33.—E. W—, female, aged 3 years 11 months.

*Present illness.*—For a fortnight previous to admission the mother noticed increase in the size of the abdomen, and for the last three days the child had complained of pain. On examination the abdomen was found to be much distended and measured 22½ inches in girth. The percussion note was dull and a fluid thrill was present. A hard swelling occupied the whole of the anterior portion of the abdomen. A distinct edge was

palpated just below the costal margin and also on the right side above the pelvic brim. The mass was slightly movable from side to side.

*Progress of case.*—The patient was under observation for over six months, and the case was complicated by an attack of diphtheria. The abdomen continued steadily to increase in size (girth 26 inches), and there was marked gastro-intestinal disturbance. A tumour of a cystic nature, giving a fluid thrill, could be definitely defined filling the whole abdominal cavity. A diagnosis of malignant cystic neoplasm was made and the cyst tapped eleven weeks after admission. A small quantity of viscid, jelly-like fluid was obtained. The patient gradually sank and died three months later.

*Pathological aspect of the case.*—A few ounces of clear mucinoid fluid were obtained from the cyst. At the time of aspiration the temperature was 99·2° F. The fluid contained 6½ grains of urea per c.c. (0·015 per cent.).

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 207 | 41·4 |
| Mononuclear neutrophilic cells | 2 | 0·4 |
| Coarsely granular polynuclear cells | 12 | 2·4 |
| Small lymphocytes | 131 | 26·2 |
| Large lymphocytes | 34 | 6·8 |
| Endothelial cells | 105 | 21·0 |
| Degenerated cells | 9 | 1·8 |
| | 500 | 100 |

A large quantity of blood was present. Five normoblasts were seen while counting 500 cells.

*Post-mortem report.*—An extremely emaciated infant with an enormously protuberant abdomen. This distension was due to a large cystic tumour filling up the whole abdominal cavity. When lifted up it was seen to arise from the left appendages by a slender pedicle and turned out to be a cystic tumour of the left ovary. It was not adherent at any point. The liver presented a secondary node about 1 inch in diameter. On further examination the tumour proved to be a cystic teratoma.

*Inoculation experiment.*—Ten c.c. of the above fluid were inoculated intra-peritoneally into a guinea-pig and the animal killed nine weeks later.

*Film from the peritoneal fluid :*

| | | Per cent. |
|---|---|---|
| Small lymphocytes . . . | 35 | 7·0 |
| Large lymphocytes . . . | 3 | 0·6 |
| Coarsely granular polynuclear cells . | 9 | 1·8 |
| Endothelial cells . . . | 453 | 90·6 |
| | 500 | 100 |

*Post-mortem examination.*—A smear from the retroperitoneal glands was examined for tubercle bacilli with a negative result. Macroscopically there was no evidence of tuberculosis in the lungs or pleura. All the abdominal organs and viscera appeared quite normal, as also did the peritoneum, glands, and mesenteries. On microscopical examination nothing abnormal was detected in the spleen or lymphatic glands.

Case 38.—Private case, X. Y— (notes furnished by Mr. L. S. Dudgeon).

On examination a tumour of the testis was found which infiltrated the substance of the gland, and spreading upwards, involved the spermatic cord. The neoplasm was diagnosed as carcinoma. At operation, when the tunica vaginalis was incised, a large quantity of turbid yellow fluid escaped.

*Pathological aspect of the case.*—Histologically the tumour proved to be a round-celled sarcoma.

*Differential count of* 500 *cells :*

| | | Per cent. |
|---|---|---|
| Small lymphocytes . . . | 61 | 12·2 |
| Large lymphocytes . . . | 6 | 1·2 |
| Endothelial cells . . . | 433 | 86·6 |
| | 500 | 100 |

Plaques of nineteen, five, and twenty-four endothelial cells were seen while counting 500 cells. There was no mitosis. Two endothelial cells showed triple nuclei, one trilobed. Many of the small mononuclear cells were a good deal smaller than the small lymphocytes of the blood and stained more deeply. There was very little protoplasm surrounding their nuclei.

Case 40.—M. G—, female, aged 23 years. No family history of tuberculosis was obtained.

*Present illness.*—Two weeks previous to admission epigastric pain commenced associated with diarrhœa. On examination a left-sided ovarian tumour was found and signs of a right pleural effusion.

*Progress of case.*—Death occurred within a few days of the fluid being withdrawn.

*Pathological aspect of the case.*—Three pints of fluid were obtained.

*Film stained by Leishman. Count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 1 | 0·2 |
| Small lymphocytes | 44 | 8·8 |
| Large lymphocytes | 1 | 0·2 |
| Endothelial cells | 454 | 90·8 |
| | 500 | 100·0 |

A second film was stained by van Gieson's method and hæmalum. Masses of cells larger than the usual endothelial placards were seen, and, owing to the shape and size of the cells and of their nuclei, malignant disease was thought to be present.

*N.B.*—The Leishman film gave no suspicion of this.

*Post-mortem report.*—A primary carcinoma of the left ovary was found. In addition there was diffuse carcinomatosis of the peritoneum and both pleuræ. There were no secondary growths in any of the viscera.

## On the Significance of the Finely Granular Polymorphonuclear Cell in Pathological Fluids.

Since Widal and Ravaut first noticed a large excess of finely granular polymorphonuclear cells in acute infective pleurisies, examples of septic meningitis, and certain other conditions, investigators have again and again verified their results.

I have obtained and tabulated[1] twelve instances of this class of case, and it will be observed that in eight of them the bacteriology has been worked out. In two cases of "postbasic meningitis" (Cases 9 and 43) the polynuclears were the principal cells in the cerebro-

[1] See Table V.

TABLE V.

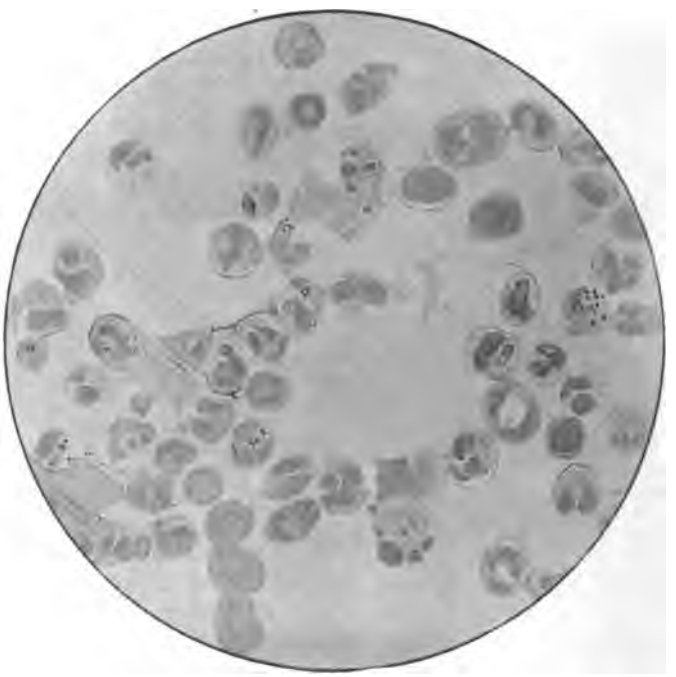
| Nature of case. No. | Remarks. | Chief cell. | Micro-organism isolated.[1] |
|---|---|---|---|
| Pneumothorax, empyema (1) | Probably tuberculous in origin, secondary infection with pyogenic organism | Polynuclear cells = 97·6 per cent. | — |
| Post-basic meningitis (9) | The ears were normal | Polynuclear cells = 67·5 per cent.; many contained diplococci | The meningococcus. |
| Septic meningitis (16) | Ears normal; a very chronic case of 8 months' duration | No cells seen | The *staphylococcus albus*. Grown from the cerebro-spinal fluid during life |
| Pleural effusion (23) | Rheumatic (?); septic (?); sudden onset with pains in the limbs and back, pyrexia and sweating; history of rheumatism | Polynuclear cells = 71 per cent. | — |
| Septic meningitis (26) | Ears normal | Polynuclear cells = 88 per cent. | The *staphylococcus albus*. Grown from cerebro-spinal fluid during life and obtained at autopsy. |
| Pleural effusion (28) | Numerous cocci and bacilli were seen in the films | Polynuclear cells = 63 per cent. | — |
| Meningitis (? cause) (32) | Discharge from the right ear | Polynuclear cells = 32·8 per cent.; lymphocytes = 41·6 per cent. | Cerebro-spinal fluid was sterile. No autopsy was allowed. |
| Pyloric carcinoma, empyema (34) | — | Polynuclear cells = 69·8 per cent. | The pneumococcus in pure culture. |
| Perforated gastric ulcer, pleural effusion, subdiaphragmatic abscess (41) | — | Polynuclear cells in large excess | — |
| Septic meningitis, subdural abscess (35) | Chronic otorrhœa; acute mastoiditis | Polynuclear cells = 91·2 per cent. | The *staphylococcus albus* in pure culture. A bacillus morphologically resembling *B. diphtheriæ* (not cultivated). |
| Post-basic meningitis (43) | Otorrhœa (?) | Enormous numbers of polynuclear cells. Inside many of them diplococci were seen | The meningococcus. |
| Empyema (44) | Suprapubic prostatectomy had been performed. The case was subsequently complicated by carbuncle and perineal abscess. At the present time (3 months later) doing well | Finely granular polynuclear cells almost exclusively. | A streptococcus was isolated, but it died out. |

[1] The bacteriology of these cases was worked out by Mr. L. S. Dudgeon at St. Thomas's Hospital.

spinal fluid, and many of them contained diplococci. One of the films has been photographed to show this phagocytic reaction.

Dr. Henry Koplik draws attention to the cytology of posterior basic meningitis,[1] and states that in most examples a "polynuclear picture" is found. In one case, however, a "mononuclear picture" was observed, and here the disease was characterised by extreme chronicity and hydrocephalus. Koplik believes that the polymorphonuclear cell had eventually given

FIG. 41.



Film preparation made from the cerebro-spinal fluid of a case of postbasic meningitis. There is a large excess of polymorphonuclear cells with included meningococci. $\frac{1}{12}$ oil immersion. Photograph of a drawing (for the use of which I am indebted to the courtesy of Dr. J. J. Perkins).

place to the lymphocyte, but there is no proof of this. Such instances should not cause difficulty, unless an examination of the cerebro-spinal fluid has been postponed till late in the disease.

In Case 34 an empyema complicated malignant stenosis of the pylorus. Previous to operation a semi-purulent fluid was

[1] 'Amer. Journ. of Med. Sci.,' vol. cxxix, p. 273.

obtained in which the polynuclear cells amounted to 69·8 per cent. It was proved by bacteriological investigation that the pneumococcus was the cause of infection. Earl, Widal, and Ravaut and others state that polymorphonuclears predominate under these circumstances; Earl adds that numerous endothelial cells may also be present, and Widal refers to the phagocytic action of the macrophages on the microphages in his example of pneumococcic pleurisy. In my case, however, only 9·8 per cent. of endothelial cells were noted.

There is no definite[1] evidence to prove that rheumatic fever has any part in the etiology of pleural effusions, but pathologists have for some time past considered this a possible hypothesis, and it is a favourite argument with those unwilling to admit the tuberculous origin of most primary "idiopathic" pleurisies.

While declining to express any opinion, I may draw attention to Case 23 as an interesting one from this point of view. It will be seen that just over 70 per cent. of polymorphonuclear cells were present.

Earl refers to "true rheumatic pleural effusions" occurring in the course of acute rheumatism and has found that in such instances the polynuclear is the chief cell.

In the literature the cytology of the cerebro-spinal fluid in acute septic meningitis has received but scant notice in comparison with the attention paid to the tuberculous and post-basic varieties. I have records of three cases and have been struck with the fact that the *staphylococcus albus* has played a part in all.

In two of the examples this seems to have been the only micro-organism present, and in both these the channel of infection was apparently not *viâ* the tympanic cavity. In the remaining case a mixed infection, originated by a chronic otorrhœa, caused death within a few days.

In two of these cases 88 and 91·2 per cent. of polymorphonuclear cells were found. In the third no cells were seen,[2] but the clinical aspect of this example was peculiar. Since its duration extended over a period of more than eight months, it cannot be described as "acute" or highly "toxic." On the other hand,

[1] Since writing the above I find that Professor Osler fully recognises a rheumatic type of pleurisy.

[2] Unfortunately, only one examination of the cerebro-spinal fluid was made.

there seems no reason to doubt that the meninges had been infected by the *staphylococcus albus*.

Dudgeon, Sargent, and Ross have all shown that as a rule large numbers of polynuclear cells appear within a very short time of infection by this micro-organism.

Case 26 may be again cited as presenting 88 per cent. of these cells, while the *staphylococcus albus* was alone isolated in pure culture both during life and at autopsy.

Although instances of septic meningitis present the same cytological picture as the "post-basic" variety, the clinical features will usually suffice for a correct diagnosis. Moreover, as the presence of the cocci *within* the cells is a characteristic feature of "post-basic" meningitis, an examination of film preparations provides an additional clue.

Case 41 calls for no special comment. It concerned an instance of sub-diaphragmatic abscess complicated by a pleural effusion, in which polynuclear cells were observed in large excess.

Example 32 is included here as it was most probably an infective case; at the same time, it must be remembered that otitis media may be due to tuberculosis, and that according to Widal the cell count would not negative such a possibility. In the light of my own experience, I should hesitate to diagnose tuberculous disease with only 41·6 per cent. of small lymphocytes.[1]

The last example in the table is one of streptococcus empyema secondary to a septic condition of the genito-urinary organs after enlargement of the prostate. Polynuclear cells were found almost exclusively in the fluid obtained a few days before the empyema developed, and long chains of streptococci were seen in the films. This organism was isolated, but died out so quickly that further identification was impossible.

My findings in these acute infective cases have only confirmed those of other authors in this department of the subject, but before passing on to the consideration of mechanical effusions I should like to briefly refer to those eosinophile pleurisies[2] described by Widal and Ravaut, and also at some length by Barjon and Cade. These latter observers have succeeded in showing that effusions in which the coarsely granular eosino-

[1] A guinea-pig was inoculated intra-peritoneally with the fluid, but died twelve days later. There was no evidence of tuberculosis.

[2] Recently I have had an opportunity of examining films from one of these cases occurring at St. Thomas's Hospital.

phile cell predominates are probably not tuberculous. They inoculated animals, and obtained negative results without exception.[1] Most of the patients also made a complete and rapid recovery; another feature was the small amount of fluid usually present, often hardly sufficient to justify thoracentesis.

It would appear that the coarsely granular eosinophilic leucocyte is confined to the early stages of infection,[2] and later on becomes replaced by some other cell (lymphocyte or finely granular polynuclear). This is a most interesting point in view of the very similar results obtained by Dudgeon and Ross in their research on phagocytosis. The eosinophilia, however, in the pleural exudate is not confined to so brief a period as the first two hours after infection,[3] and it is doubtful if a chest has ever been aspirated within four hours of determining the presence of a commencing effusion.

Case 1.—J. G—, male, aged 39 years. A family history of tuberculosis was obtained on the mother's side.

The *present illness* was of sudden onset with severe left-sided pain. After a time this passed away, and was replaced by cough, a feeling of fulness in the chest, and dragging sensations. On physical examination a left-sided pyopneumothorax was found. The patient was aspirated, and 37 oz. of turbid, greenish fluid were withdrawn.

*Progress of the case.*—Ten days after admission pus was detected and the patient operated on for empyema. After a stay in hospital of over six months the patient went home nearly well with only a very slight discharge from the operation sinus.

*Temperature-chart.*—For twenty-two weeks after admission there was irregular pyrexia ranging from 100° to 102° F. in the evening and becoming normal, or subnormal, in the morning. On discharge there had been a normal temperature for many days.

*Report by the patient.*—No further information could be obtained.

*Pathological aspect of the case.*—Pleural effusion: at the time of aspiration the temperature was 99° F. The fluid withdrawn was turbid; it did not resemble pus, but could not be compared with a serous effusion (37 fluid oz.).

[1] Widal and Ravaut found this same fluid highly toxic to guinea-pigs.

[2] Barjon and Cade.

[3] "Phagocytosis," Dudgeon and Ross, 'Path. Soc. Trans,' London, Aug., 1906.

*Differential count of 500 cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 488 | 97·6 |
| Small lymphocytes | 4 | 0·8 |
| Large lymphocytes | 3 | 0·6 |
| Endothelial cells | 5 | 1·0 |
| | 500 | 100·0 |

All the finely granular polynuclear cells were much degenerated. No micro-organisms were seen. Film preparations from the empyema fluid consisted of pus only. Repeated examinations of the sputum for tubercle bacilli were negative.

Case 9.—H. H—, male, aged 1½ years.

*Present illness.*—Attacks of convulsions associated with vomiting had been present for four weeks previous to admission; head retraction was also noted. On coming into the hospital the patient was in a semi-comatose state and resented being moved.

On physical examination the pupils reacted normally; there was slight optic neuritis. There was spasm of the flexors of the thigh on the left side and Kernig's sign was marked. The knee-jerks were brisk on both sides and equal. There was no ankle-clonus and the plantar reflex was of the infantile type. The tympanic membranes were normal.

*Progress of case.*—Internal strabismus developed with very marked head-retraction. The patient continued in a semi-conscious state and emaciated rapidly. Three weeks after admission lumbar puncture was performed and 4 drms. of clear cerebro-spinal fluid obtained. Death took place nine weeks after admission. At first the lesion was thought to be tuberculous, but later hydrocephalus developed and a diagnosis of post-basic meningitis was made.

*Temperature-chart.*—For some weeks irregular pyrexia was present, but the temperature seldom rose above 101° F.; during the last fortnight of life there was a steady fall towards the normal.

*Pathological aspect of case.*—Cerebro-spinal fluid. At the time of lumbar puncture the temperature was 100·2° F.; 4 drms. of clear fluid were obtained.

*Differential count of* 200 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 135 | 67·5 |
| Small lymphocytes | 52 | 26·0 |
| Large lymphocytes | 8 | 4·0 |
| Large hyaline cells | 5 | 2·5 |
| | 200 | 100·0 |

Many of the polynuclear cells and of the large hyalines were phagocytic. Small diplococci were seen within them.

*Post-mortem report.*—An emaciated child with a gaping anterior fontanelle. The head measured 18 inches in circumference. The dura mater was thickened, the brain distended, and the convolutions flattened. The pial roof of the fourth ventricle was very much thickened, as was also the pia over the interpeduncular space. On opening the lateral ventricles it was found that a fair amount of brain-tissue was present, in spite of considerable distension of the posterior horns. There was no exudate, nor was there any sign of recent inflammation. There was no evidence of sclerosis of the brain-substance, nor were there any macroscopic changes in the ependyma. The great venous sinuses and the ears were healthy.

Case 16.—S. L—, male, aged 23 years. No family history of tuberculosis was obtained.

*Present illness.*—The onset was insidious, with headache, and irregular vomiting. There was no history of trauma or fits. A routine investigation failed to show any evidence of organic nervous disease. Some tenderness was found over the lower part of the occiput and upper cervical region. There was no mastoiditis.

*Progress of the case.*—This patient continued under observation and treatment for the greater part of eight months. Ten days after admission the presence of optic neuritis was detected. On trephining no tumour was found in the frontal region. Subsequently hernia cerebri developed with signs of increased intra-cranial pressure and a lumbar puncture was performed. There was some trouble with the speech and loss of power to a certain extent in the right arm. The patient was discharged for a short time at the end of five months with the hernia cerebri still persisting. On his return it was noted that a large

hernia cerebri remained and that the speech was limited to "yes" and "no." The optic discs were now atrophic. A second operation failed to reveal any neoplasm, and shortly afterwards death occurred with the onset of persistent vomiting.

*Temperature-chart.*—There was no notable rise of temperature above the normal except when the lumbar puncture was performed.

*Pathological aspect of the case.*—The cerebro-spinal fluid was examined bacteriologically. Films direct from the fluid showed Gram positive cocci and a pure culture of the *staphylococcus albus* was subsequently obtained. Examination of films for the presence of cells was negative.

*Post-mortem examination.*—A globular tumour, which fluctuated, was found projecting from the left parietal region. On incision a large quantity of fluid gushed out and the left lateral ventricle was exposed through the fluid sac of the tumour. On removal of the brain the right lateral ventricle was moderately distended and contained yellow gelatinous pus in its recesses; similar appearances were also present in the other cranial ventricles. Most of the cortex of the left parietal and frontal lobes was soft and herniated. Careful search in all parts of the brain and cerebellum failed to reveal any neoplasm. Certain minor lesions were also noted.

CASE 23.—F. W—, male, aged 29 years. A family history of rheumatism was obtained.

*Present illness.*—Three weeks previously he complained of pains in the limbs and back accompanied by fever and sweating. On examination signs of a small amount of fluid were found at the base of the right lung. These gradually increased until a month later 40 oz. of fluid were withdrawn.

*Progress of case.*—After a stay of nine weeks in hospital this patient gradually made a complete recovery.

*Temperature-chart.*—For fourteen days after admission the temperature varied between 102° and 100° F.; during the next three weeks it gradually fell to the normal, and for the last month there was no pyrexia.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the temperature was 101·5° F.; 40 oz. of turbid greenish-yellow fluid were obtained. The specific gravity was 1012,

alkaline reaction, and on applying the boiling test almost complete solidification occurred.

*Differential count of 500 cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 355 | 71 |
| Small lymphocytes | 140 | 28 |
| Large lymphocytes | 4 | 0·8 |
| Large hyaline cells | 1 | 0·2 |
| Coarsely granular polynuclear cells | 0 | 0·0 |
| | 500 | 100·0 |

The finely granular polynuclear cells required an oil-immersion lens to differentiate them from small lymphocytes. Widal's reaction was done three times and proved negative in every instance. An examination of the blood showed that the finely granular polynuclear cells were three and a half times more numerous than in normal blood. There were large numbers of platelets in clumps and fibrin-formation was excessive. A culture taken from the pleuritic effusion was sterile.

*Inoculation experiment.*—Ten c.c. of the fluid were inoculated intra-peritoneally into a guinea-pig, which died the next morning. On macroscopic examination there were no signs of peritonitis and all the organs appeared healthy. The abdomen contained a quantity of slightly turbid fluid.

*Films from the peritoneal fluid:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 257 | 51·4 |
| Small lymphocytes | 20 | 4·0 |
| Coarsely granular polynuclear cells | 1 | 0·2 |
| Endothelial cells | 222 | 44·4 |
| | 500 | 100·0 |

*Post-mortem examination.*—Microscopically nothing abnormal was found in any of the tissues or viscera.

Case 26.—A. L—, female, aged 1¼ years. No family history of tuberculosis was obtained.

*Present illness.*—Twelve days before admission the eyes were noticed to be fixed and staring; there was also some twitching of the mouth. The child was restless, but slept well. A day or two later head-retraction was noticed. There were no fits, and

the ears were normal. On examination the cranial nerves were normal, and there was no optic neuritis. The back was slightly arched and the neck muscles were stiff. The knee-jerks were exaggerated, and the plantar reflex was of the extensor type on the right side. The anterior fontanelle was widely opened, but neither bulging nor depressed.

*Progress of case.*—Within a period of ten days lumbar puncture was performed three times. The duration of illness was five weeks and terminated fatally.

*Temperature-chart.*—For the first four weeks after admission the temperature was of the septic type. Just before the three lumbar punctures were performed 101°, 103·2°, and 102° F. were registered. For the last ten days of life the readings varied from slightly subnormal to 100·8° F.

*Pathological aspect of the case.*—Examination I: 8 drms. of finely turbid cerebro-spinal fluid were obtained. Film preparations from a broth culture showed cocci, diplococci, and staphylococci, which were Gram positive. Fourteen finely granular polynuclear cells and two endothelial cells were seen while examining two films. The micro-organism present was identified as the *staphylococcus albus* in pure culture. Examination II: 5 drms. of cerebro-spinal fluid were withdrawn.

*Differential count of* 100 *cells:*

| | |
|---|---|
| Finely granular polynuclear cells | 88 |
| Small lymphocytes | 3 |
| Endothelial cells | 3 |
| Degenerated cells | 6 |
| | 100 |

No micro-organisms were seen. Diphtheria bacilli were found in film preparations from the fauces.

*Post-mortem report.*—There was obvious distension of the cerebral hemispheres with flattening of the convolutions. There were considerable adhesions at the base in the region of the cisterna magna. The whole ventricular system was much distended and full of turbid fluid. The inflammation was most intense in the posterior fossa, and had extended forwards to the middle fossa and backwards down the cord. The upper respiratory passages were carefully examined, and showed no signs whatever of diphtheria. A culture was taken with aseptic

precautions from the cerebro-spinal fluid, from which the *staphylococcus albus* was subsequently isolated.

CASE 28.—S. T—, female, aged 40 years. No family history of tuberculosis was obtained. Three years ago there was an attack of winter cough, which became chronic.

*Present illness.*—Five weeks previous to admission the cough became worse, and there was a large quantity of sputum, and for twenty-one days there had been pain in the left side. On physical examination a large left-sided pleural effusion was found. On aspiration 16 oz. of fluid were withdrawn.

*Progress of case.*—The patient gained weight and left the hospital convalescent except for some slight signs of thickened pleura.

*Temperature-chart.*—At first there was pyrexia varying between 102·4° F. in the evening and 99° F. in the morning. The temperature was normal for a fortnight before discharge.

*Further report.*—A fortnight after discharge she was admitted to Rotherhithe Infirmary, and died there in a few days. (Could not be identified.)

*Pathological aspect of the case.*—At the time of aspiration the temperature was 101·2° F.; 16 oz. of straw-coloured fluid were obtained. Specific gravity 1008, alkaline reaction; on applying the boiling test solidification occurred.

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 315 | 63·0 |
| Small lymphocytes | 78 | 15·6 |
| Large lymphocytes | 5 | 1·0 |
| Large hyaline cells | 0 | 0·0 |
| Endothelial cells | 2 | 0·4 |
| Degenerated cells | 100 | 20·0 |
| | 500 | 100·0 |

This count is not strictly accurate as so many of the leucocytes were degenerated. Numerous cocci and bacilli were seen in the films. The sputum was examined for tubercle bacilli with a negative result.

CASE 32.—L. F—, female, aged 6 years. For one year the patient had grown emaciated and for two months previous to

admission there had been intermittent pain, deafness, and discharge from the right ear.

*Present illness.*—There had been vomiting and headache for four days. The child was restless, cried out from time to time, rather drowsy, and constantly sick. On examination the cranial nerves and the reflexes were found to be normal. There was no motor paralysis. The retinal veins were full, and the optic discs slightly swollen, the vessels kinking at their edges. There was no head-retraction.

*Progress of case.*—The slight rigidity of the limbs present on admission became increased and the right knee-jerk was brisk. Kernig's sign also developed. Four days before death a series of convulsive fits occurred which terminated in death. Lumbar puncture was performed twice.

*Temperature-chart.*—The morning record was 99·2° and this rose to 101° F. in the evening on most days.

*Pathological aspect of the case.* — At the time of lumbar puncture the temperature was 100·2° F.; 14 c.c. of clear cerebro-spinal fluid were obtained with a slight sediment.

| *Differential count of* 500 *cells:* | | Per cent. |
|---|---|---|
| Small lymphocytes | 175 | 35·0 |
| Large lymphocytes | 33 | 6·6 |
| Finely granular polynuclear cells | 164 | 32·8 |
| Coarsely granular polynuclear cells | 1 | 0·2 |
| Large hyaline cells | 1 | 0·2 |
| Degenerated cells | 126 | 25·2 |
| | 500 | 100·0 |

Most of the degenerated cells were probably polynuclears. A broth culture from the cerebro-spinal fluid proved to be sterile.

*Post-mortem report.*—Unfortunately, no examination was permitted.

*Inoculation experiment.*—Ten c.c. of the fluid obtained were inoculated intra-peritoneally into a guinea-pig. The animal died twelve days later.

| *Film from the peritoneal fluid.* | | Per cent. |
|---|---|---|
| Endothelial cells | 481 | 96·2 |
| Finely granular polynuclear cells | 3 | 0·6 |
| Small lymphocytes | 15 | 3·0 |
| Coarsely granular polynuclear cells | 1 | 0·2 |
| | 500 | 100·0 |

There was a fair amount of free fluid present in the peritoneal cavity.

*Post-mortem examination.*—No microscopic or macroscopic evidence of tuberculosis was found in any of the viscera or glands.

CASE 34.—N. S—, male.

*Present illness.*—For two years there had been epigastric pain and vomiting. On physical examination a mass was found just to the right of the middle line and about one inch above the umbilicus.

*Progress of case.*—On operating a carcinoma of the pylorus was found, which was dealt with by gastrojejunostomy. Seven weeks later signs of fluid at the base of the left lung developed. An empyema was suspected and aspiration performed; 2 pints 3 oz. of purulent fluid were obtained. The patient gradually sank and died eleven weeks after admission.

*Temperature-chart.*—The temperature was normal till the empyema occurred, when there was irregular pyrexia for nine days.

*Pathological aspect of the case.*—At the time of aspiration the temperature was 101·8° F.; 2 pints 3 oz. of almost purulent fluid were obtained. The reaction was alkaline, the specific gravity 1016, and on applying the boiling test solidification occurred.

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 349 | 69·8 |
| Small lymphocytes | 101 | 20·2 |
| Endothelial cells | 49 | 9·8 |
| Large lymphocytes | 1 | 0·2 |
| | 500 | 100·0 |

Cultures were taken from the fluid and in them the pneumococcus isolated.

CASE 35.—A. S—, male, aged 24 years.

*Present illness.*—There was a history of chronic otorrhœa for three years. This had been worse for ten days, and there had been acute symptoms for three days previous to admission. For six days the discharge had ceased, but appeared again on the seventh day, accompanied by severe rigors. There was very

obvious pain on making pressure over the base of the mastoid, but no œdema. The optic discs were normal.

Immediate operation was decided upon, and pus was found in the mastoid antrum, attic, and central cells. No evidence of lateral sinus thrombosis.

*Progress of case.*—Two days later coma and stertorous breathing supervened. At a second operation pus was evacuated by a trocar from the brain and 6 oz. of clear fluid obtained by lumbar puncture. The patient died on the table.

*Temperature-chart.*—This showed variations between 101·3° and 105·6° F. and was pyæmic in type.

*Pathological aspect of the case.*—At the time of lumbar puncture the temperature was 105° F.; 6 oz. of slightly turbid fluid were obtained.

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 456 | 91·2 |
| Large lymphocytes | 8 | 1·6 |
| Endothelial cells | 2 | 0·4 |
| Small lymphocytes | 34 | 6·8 |
| | 500 | 100·0 |

Most of the finely granular polynuclear cells showed signs of degeneration.

*Result of bacteriological examination of cerebro-spinal fluid.*—Large numbers of phagocytes were present in the turbid fluid from the spinal canal, also groups of staphylococci and a bacillus morphologically resembling the diphtheria bacillus. A pure culture of the *staphylococcus albus* was obtained from cultures of the fluid. The bacillus was not grown.

*Post-mortem report.*—A small abscess was found on the under surface of the left temporo-sphenoidal lobe, which had ruptured into the descending cornu of the left lateral ventricle, thus infecting the system on the left side. The inflammation had extended backwards to the fourth ventricle along the iter and thence to the cisterna magna, thus producing a post-basic meningitis. The great sinuses were examined and found not to be thrombosed.

Case 41.—M. J—, female, aged 37 years.

*Present illness.*—Abdominal pain, discomfort, and vomiting

after food had been present for eight months. Fourteen days before admission there had been intermittent abdominal pain, with sickness and diarrhœa.

On examination a very tender mass was found in the umbilical region. At operation a perigastric abscess, due to a perforated gastric ulcer, was discovered.

*Progress of case.*—The patient progressed favourably for four weeks, after which a rigor occurred, and signs of a left-sided effusion into the pleural sac were found. Aspiration was performed and 10 oz. of clear fluid withdrawn. Next day a second aspiration produced a negative result; the subdiaphragmatic region was then explored, and a large offensive abscess cavity opened up.

*Temperature-chart.*—For the first fortnight after the primary operation the temperature was often subnormal, and there was no elevation above 100° F. During the succeeding four weeks the chart assumed the suppurative type, and four rigors occurred. During this period the chest was aspirated and the subdiaphragmatic abscess opened.

*Pathological aspect of the case. Pleural effusion.*—At the time of aspiration the temperature was 105·8° F.; 10 oz. of clear fluid were obtained.

*Report on the nature of the cells.*—The cells consist entirely of finely granular polymorphonuclears and endothelial cells. The former variety was in large proportion.

Case 43.—M. E. A—, female.

*Present illness.*—Fourteen days previous to admission the mother had noted that the head was bent backwards, and that the spine was dorsiflexed. Five days later a dark brown discharge from the ears and the presence of strabismus were noted. On physical examination it was found that the head was markedly retracted, and the whole spine bent backwards. The anterior fontanelle was wide open and bulging. No strabismus was detected. The pupils were equal, and reacted sluggishly to light. There was no paralysis of any of the limbs. The knee-jerks were present and equal, and on plantar stimulation there was a generalised response. Examination proved the optic discs to be normal.

*Progress of case.*—About a week later strabismus developed,

and there was increased head-retraction. The fontanelle was still bulging. Lumbar puncture was performed, and 10 oz. of opalescent fluid were obtained. The patient at the time of writing was still under observation.

*Temperature-chart.*—For the first fortnight that the patient was in hospital the temperature was subnormal, except for a period of three days when it varied between 99·4° and 101·6° F. There then ensued a further period of four days when it varied between 100·8° and 102·4° F.

*Pathological aspect of the case.*—At the time of performing lumbar puncture the temperature was 99° F.

*Result of examination of the cerebro-spinal fluid.*—The specimen of fluid was turbid. Enormous masses (at least 90 per cent.) of phagocytes were seen, chiefly of the polynuclear type. Numerous diplococci were seen inside these cells. Cultures were taken and the meningococcus isolated.

Case 44.—J. C—, aged 56 years. There had been difficulty in micturition for seven years. Suprapubic prostatectomy had been performed with much benefit.

*Present illness.*—About a fortnight after his discharge he complained of pain in the chest, especially severe on the right side, and cough. Later dyspnœic attacks occurred. On examination a right-sided pleural effusion was found, which was aspirated. Empyema followed.

*Progress of case.*—Carbuncles and a perineal abscess occurred. Notwithstanding, the patient is now (three months later) very much better and still under treatment.

*Temperature-chart.*—Pyrexia of the septic type was present for a long time, but latterly there had been a marked fall in the continuity of the curve towards the normal.

*Pathological aspect of the case.*—Sixteen oz. of fluid were obtained. At the time of aspiration the temperature was 103·4° F.

*Cell count.*—Polymorphonuclear cells were present almost exclusively. Long chains of streptococci were seen in the films.

*Bacteriological examination.*—A streptococcus present in the exudate. Organisms were seen in very large numbers in the film preparations of the fluid, also numerous phagocytes. Nature of streptococci impossible to determine as they died out, owing to the presence of air organisms in the original tube.

### The Cytology of Mechanical Effusions.

Widal and Ravaut in their original monograph class as "mechanical" those painless and often rapid pleural effusions which occur in the terminal stages of cardiac and renal disease. This outpouring of fluid is usually attributed to increased venous pressure, with engorgement of the right heart and great vessels. Be this as it may, the cytological aspect of the fluid in these examples is very different from that which obtains in tuberculosis or acute infective processes.

Endothelial cells are found to be present almost exclusively and are often aggregated into plaques. Widal and Ravaut account for the absence of these cells in tuberculosis by supposing that the formation of a tuberculous membrane prevents any desquamation taking place. They further state that numerous endothelial cells point to a "mechanical" effusion, notwithstanding the presence of small lymphocytes and polymorphonuclears.

I have been unable to examine the pleural fluid in a case of pure hydrothorax, but am acquainted with some experimental work which goes far to support Widal's observations.

In a paper on acute diphtheritic toxæmia just recently read by Mr. L. S. Dudgeon before the Neurological Society of London, the author gives an account of the cytology of the pleural fluid in guinea-pigs dying in this state with marked cardiac failure. An excess of endothelial cells was found in every instance, and they were often massed together into plaques. The condition was strictly equivalent to a hydrothorax, and the cytological

Table VI.

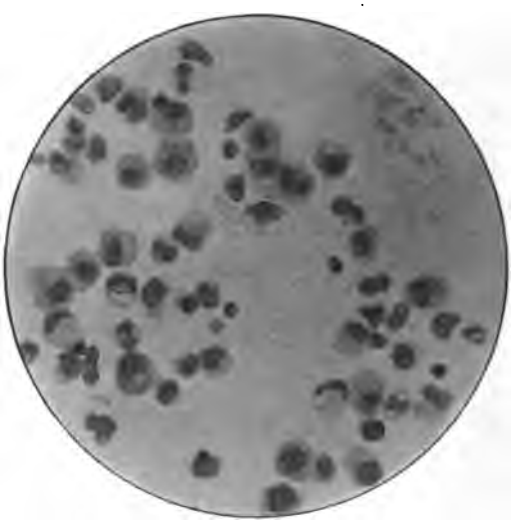
| Nature of case. | Principal cell. |
|---|---|
| Cirrhosis of liver; alcoholic and syphilitic histories obtained (22). Negative inoculation experiment. | Endothelial cells = 78·6 per cent. |
| Cirrhosis of liver (21) . . . | Endothelial cells = 95·4 per cent. |
| Cirrhosis of liver. Provisional diagnosis was tuberculous peritonitis (7). | Endothelial cells = 61 per cent. |
| Chronic peritonitis. Ovarian cyst previously removed. | Endothelial cells = 97 per cent. |
| Cirrhosis of liver (25). . . . . | Endothelial cells = 26 per cent. small lymphocytes = 33 per cent. |
| Chronic hydrocele (3). . . . | No cells seen. |
| Chronic hydrocele (15) . . . | Endothelial cells = 95·2 per cent. |

findings agreed with those of Widal and Ravaut under similar circumstances in the human subject.

In Table VI four cases of hepatic cirrhosis are recorded, and in three of them a large excess of endothelial cells was present. This is a feature to be expected, since the accumulation of ascitic fluid is due to mechanical obstruction of the portal vein and its tributaries.

For similar reasons a case of carcinoma of the liver, already dealt with, showed a cell-count in which endothelial elements

FIG. 42.



A film preparation, consisting almost entirely of endothelial cells. Made from the ascitic fluid in a case of hepatic cirrhosis. $\frac{1}{6}$th.

predominated. One or two inoculation experiments were performed with the fluid obtained from the cases now under consideration. *In every instance it proved to be harmless.* Film preparations were made from the peritoneal fluid of the guinea-pigs used, and these showed no departure from the normal cytology.

Much difference of opinion exists among writers as to the value of cell-counts in cirrhosis of the liver and allied conditions. Barjon and Cade consider the results are too variable to be of much value for the cytodiagnosis of ascites. I am compelled to differ from them in this estimate of the value of their results, which are satisfactory enough. In two cases of alcoholic cirrhosis and

in one of ovarian cyst, all with ascites, they found that the endothelial was the chief cell. In two examples of tuberculous peritonitis there was a marked lymphocytosis in the peritoneal fluid. Earl finds that the ascitic fluid produced in cases of hepatic cirrhosis contains endothelial cells, as a general rule, with the addition of a moderate number of polynuclears and a few small lymphocytes.

It might be thought that as "the endothelial picture" is so constant in cirrhosis of the liver, no useful purpose would be

FIG. 43.

Film made from the ascitic fluid in a case of hepatic cirrhosis. It shows the usual size of endothelial plaque commonly met with in this and kindred conditions. One cell presents a large vacuole. $\frac{1}{8}$th.

served by making these examinations. In reality, however, the importance of a cell-count cannot be over-estimated. We have the good authority of Dr. Hale White and others for stating that tuberculous peritonitis is a frequent complication of hepatic cirrhosis.[1] In the cases I happen to have examined cytologically the inoculation experiments may be taken as proving that this complication did not exist.

In such an example the endothelial cells should be to a large extent replaced by lymphocytes. This is a point of great interest and one deserving of further investigation.

[1] See Allchin, 'A Manual of Medicine,' vol. v.

Cytodiagnosis proves its value in such an instance as Case 7[1] of Table VI. A provisional diagnosis of tuberculous peritonitis had been made. There were 61 per cent. of endothelial cells present in the ascitic fluid. In a short time it became evident clinically that the case was not one of tuberculous peritonitis, and this was further supported by a negative inoculation experiment.

Case 25 produced the following cell-count:

| | | Approximate percentage. |
|---|---|---|
| Finely granular polynuclear cells . | 40 | 24 |
| Small lymphocytes . . . | 55 | 33 |
| Large lymphocytes . . . | 15 | 8 |
| Coarsely granular polynuclear cells | 11 | 7 |
| Endothelial cells . . . | 42 | 26 |
| | 163 | 98 |

The case was diagnosed as cirrhosis of the liver; colicky pains and diarrhœa were marked. The liver edge could not be felt and there was no pyrexia. As far as cytology goes this example is not suggestive of cirrhosis. Unfortunately, no animal experiment was performed, and it is an open question whether the case was not one of tuberculous peritonitis, possibly with cirrhosis superadded. In this event I should have expected rather more than 41 per cent. of lymphocytes.

No less than 97 per cent. of endothelial (?) cells were found in a case of chronic peritonitis associated with ovarian cyst, which latter had been removed some time previously.[2] A painting has been made to show the extraordinary size of the cells present and the multiple nuclei contained in many of them. It is to be noted that no evidence of malignancy in the shape of mitotic figures could be demonstrated in any of the cells.

A similar example is quoted by Barjon and Cade, but they make no mention of any special features regarding the cells.

It is necessary to record the fact that Dopter and Tanton in a typical instance of hepatic cirrhosis found large numbers of finely granular polymorphonuclear cells and very few endothelial elements. This anomaly is probably accounted for by the

[1] Hepatic cirrhosis.

[2] The term "endothelial," as applied to these cells, is really a misnomer. Mr. Shattock, who has examined the painting, suggests that probably one of the loculi of the cyst (containing papillomatous growths) had ruptured, and that these peculiar cells have this origin.

## EXPLANATION OF PLATE IV,

Illustrating the communication on "Cytodiagnosis," by Dr. E. A. Ross. (P. 361.)

FIG. 1.—Reproduction of a painting from a film preparation of the pleural fluid in Case 40. The primary growth was a left ovarian carcinoma, and there was secondary involvement of the peritoneum and of both pleural sacs, with effusion into the right. Duration of illness uncertain. Note the large masses of coherent cells and the presence of many large cells with multiple nuclei, which appear to have been derived from the fusion of several smaller cells. Stained by van Gieson and hæmalum.

FIG. 2.—Film preparation from the ascitic fluid of Case 42. The patient was a woman, aged 59 years. Duration of illness about fifteen months. She suffered from chronic peritonitis, and had a multilocular ovarian cyst removed, one year before this film was made.

The cells are notable for their enormous size and multiple nuclei. They resemble in general characteristics endothelial cells, but should probably not be classed as such (see text). Leishman's stain.

Fig 1

Fig 2.

## EXPLANATION OF PLATE IV.

Fig. 1.

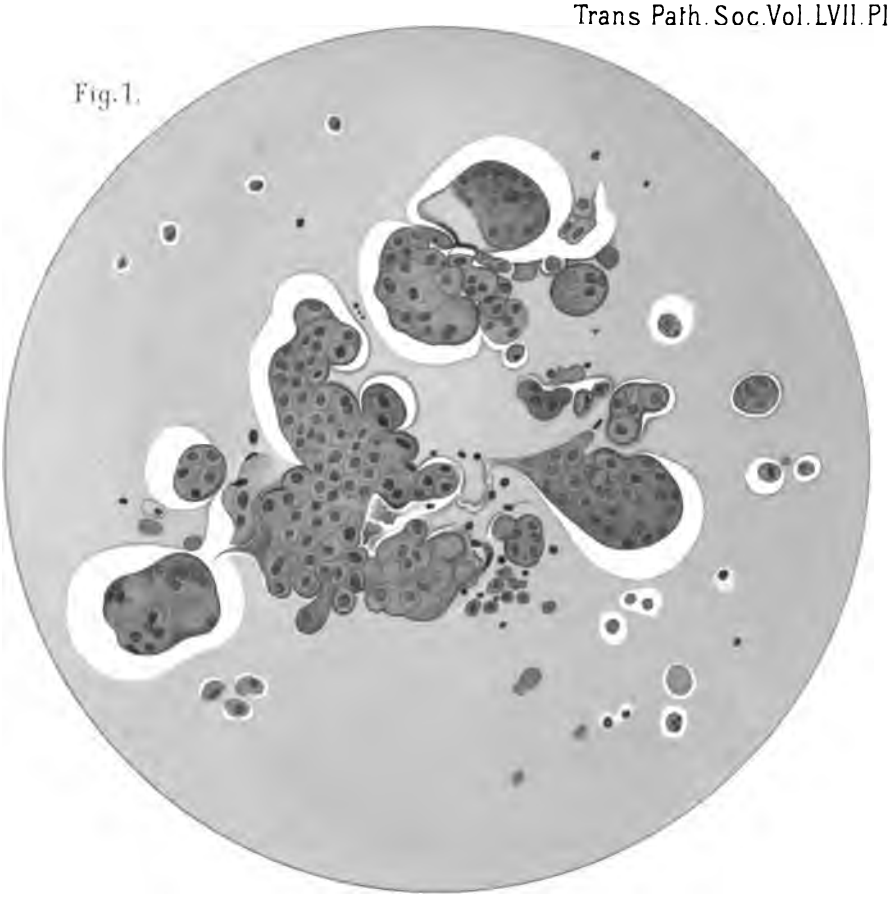
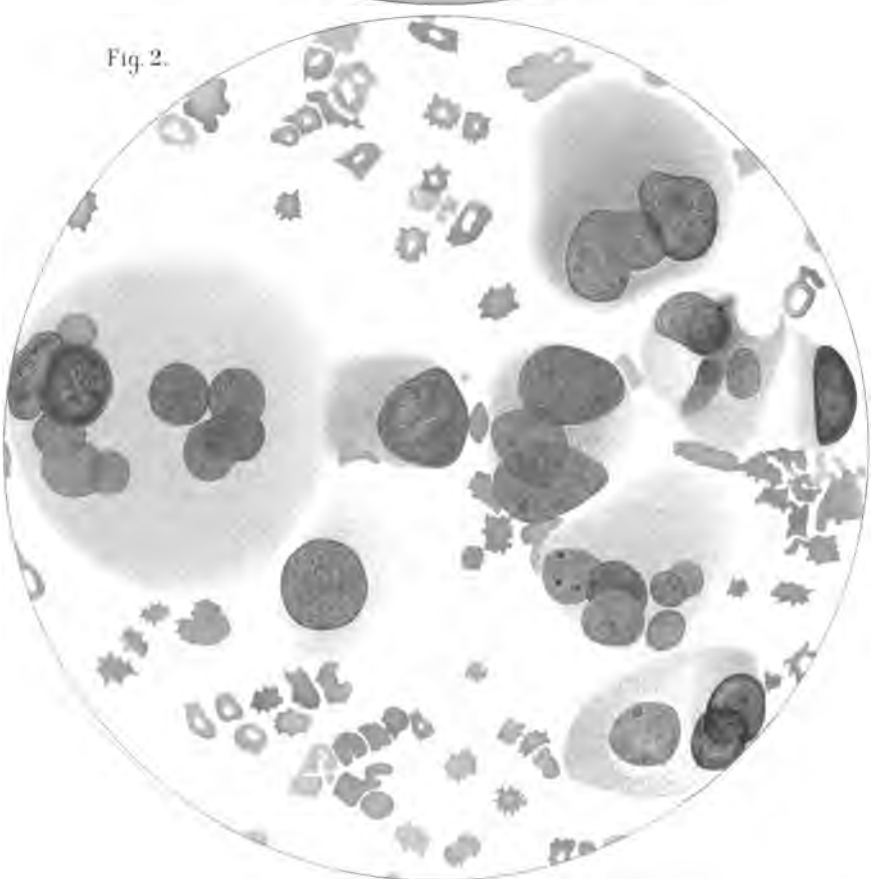


Fig. 2.



presence of some acute inflammatory reaction in addition to the mechanical effects of pressure on the portal vessels. At any rate, this class of case is quite exceptional, for in the vast majority of examples hepatic cirrhosis is characterised by an excess of endothelial cells.

I have obtained no case of tuberculous peritonitis that could be included in my series, but within the last few days one was observed in which the small lymphocyte predominated. Those who have done cell counts on the exudate in tuberculous infection of the peritoneum all testify to the presence of large numbers of small lymphocytes, and I should unhesitatingly endorse this view from what I have myself observed *in experimental work*.

So much has been written on the cytology of chronic hydrocele fluid (tuberculous disease being excluded) that I feel it is impossible to comment on the two cases included in my table, except to say that my results tally with those of other writers.

When a mechanical cause is the only one producing an outpouring of fluid into a serous sac the cytology of that fluid will be characterised by the predominance of endothelial cells.

CASE 3.—J. B—, male, aged 37 years. Out-patient. No family history of tuberculosis was obtained. The patient complained of a right-sided hydrocele of six years' standing. Onset soon after an attack of gonorrhœa, which was not complicated by epididymitis or orchitis. This hydrocele had been repeatedly tapped before the films were taken. After operation the cord and testicle appeared normal. Ten c.c. of pale, straw-coloured fluid were obtained.

*Negative result.*—No cells were found on six films examined and no spermatozoa were seen.

*Report by the patient.* — No further information could be obtained.

CASE 7.—A. W—, male, aged 45 years. No family history of tuberculosis was obtained. The patient took 1½ pints of alcohol *per diem* for the last ten years.

*Present illness.*—For a week before admission there had been abdominal pain, which was worse on coughing. Vomiting had been usual in the morning for a month. The patient was constipated. On physical examination free fluid was found in the abdomen and the liver edge could be felt on "dipping."

A provisional diagnosis of tuberculous peritonitis was made and paracentesis abdominis performed. Six pints of fluid were withdrawn, after which a firm liver edge was easily palpable and the surface of the viscus was found to be smooth. The heart and kidneys were normal.

*Progress of case.*—Under observation it became apparent that the case was cirrhosis of the liver. Six weeks after the first admission the man was readmitted with a fresh collection of fluid in the abdomen. Two operations were performed within eight days of each other and 13½ and 16 pints respectively were withdrawn. The liver was now found to be somewhat nodular on the surface. Eventually the patient was well enough to be discharged.

*Temperature-chart.*—During the whole of the first observation the temperature remained normal. During the second course of treatment the chart showed a normal temperature every morning with a slight nocturnal elevation to 100·5° F.

*Pathological aspect of the case.*—The ascitic fluid was straw-coloured and slightly turbid; on boiling after acidulation a heavy trace of albumen was present. The specific gravity was 1012. On readmission, however, the fluid became almost solid on applying the boiling test.

*Film from the ascitic fluid. Count of* 500 *cells :*

| | | Per cent. |
|---|---|---|
| Endothelial cells | 305 | 61 |
| Small lymphocytes | 73 | 14·6 |
| Large lymphocytes | 42 | 8·4 |
| Large hyaline cells | 64 | 12·8 |
| Finely granular polynuclear cells | 13 | 2·6 |
| Coarsely granular polynuclear cells | 3 | 0·6 |
| | 500 | 100·0 |

The cells were very numerous. No mitotic figures were seen. The preponderance of endothelial cells so absolutely negatived tuberculosis that an inoculation experiment was not made at first. Later on one was performed and the animal killed after eight weeks. No evidence of tuberculosis was found.

Case 15.—R. J—, male, aged 71 years, out-patient. This patient was suffering from chronic left-sided hydrocele. No family history of tuberculosis was obtained, and there had been

no venereal disease or traumatism. The hydrocele had been tapped six times. After tapping the sac was so thick as to obscure the cord and its connections entirely. The testicle was fairly well palpated and there appeared to be no gross disease.

*Report by patient.*—Ten months later the fluid was only slowly reaccumulating.

*Pathological aspect of the case. Hydrocele fluid.*—On tapping 15 c.c. of clear pale yellow fluid were obtained.

*Differential count of* 500 *cells :*

| | | Per cent. |
|---|---|---|
| Endothelial cells . . . | 476 | 95·2 |
| Small lymphocytes . . . | 24 | 4·8 |
| | 500 | 100·0 |

No micro-organisms and no spermatozoa were seen. Many of the endothelial cells were in placards.

Case 21.—R. L—, male, aged 53 years. No history of tuberculosis, cancer, rheumatism, or gout was obtained.

*Present illness.*—For five months previous to admission the patient complained of malaise, chronic diarrhœa, and loss of weight. On going to bed one night he felt some pain in his neck, and the next morning his left arm from the elbow to the hand was much swollen and also painful.

On examination dilated veins were found over the left anterior aspect of the chest and in the left axilla; the axillary vein on that side was thrombosed. Distended veins were also present over the abdomen, and physical signs of ascites were obtained. Paracentesis abdominis produced 46 oz. of fluid. The liver edge could not be felt either before or after operation.

*Urine.*—Heavy trace of albumen, blood-cells, hyaline and granular casts.

*Progress of case.*—The patient left hospital with evidence of a small quantity of free fluid in the abdomen.

*Temperature chart.*—There was some irregular pyrexia during the time that patient was kept under observation; the temperature varied between 100·6° F. and 97° F.

*Pathological aspect of the case.*—Forty-six ounces of pale green fluid were obtained. Reaction alkaline; specific gravity 1008. On boiling, three quarters albumen was present.

*Differential count of* 500 *cells :*

| | | Per cent. |
|---|---|---|
| Endothelial cells | 477 | 95·4 |
| Small lymphocytes | 22 | 4·4 |
| Finely granular polynuclear cells | 1 | 0·2 |
| | 500 | 100·0 |

Placards of 22, 98, and 47 endothelial cells were seen while counting 500 cells. A feature was the universal predominance of the endothelial type of cell.

Case 22.—H. G—, male, aged 36 years. Two and a half years previous to readmission the patient had been under treatment for syphilitic disease of the liver. Iodides were administered with benefit and a period of fairly good health ensued. He was addicted to the use of alcohol.

*Present illness.*—For some weeks there had been increasing discomfort, due to enlargement of the abdomen. On examination so much fluid was present in the abdominal cavity that palpation of the viscera was impossible. Subsequently the liver was found to be hard and smooth; it reached to the level of the umbilicus. The spleen also extended two inches below the costal margin; 124 oz. of fluid were withdrawn.

*Progress of case.*—The patient was treated for over three months, during which period paracentesis abdominis was performed ten times. The blood was examined once, but presented no abnormal features. One month after admission a small pleural effusion at the base of the right lung was aspirated.

*Temperature-chart.*—On one or two occasions there was a slight rise above the normal.

*Report by the patient.*—Eight months later the patient wrote to say he had been under treatment at another hospital. Adrenalin injections had been tried without effect, and abdominal exploration had just been undertaken with slight improvement subsequent to operation.

*Pathological aspect of the case.* — On paracentesis 6 pints 4 oz. of turbid yellowish fluid were obtained, reaction alkaline, specific gravity 1010; on boiling partial solidification took place. The second time the fluid was removed it so strongly suggested chyle that several examinations were made.

*Chemical properties of the fluid.*—Three separate reports were made at different times, as follows:

(1) "Nature and result of examination of the peritoneal fluid: Turbid, alkaline, specific gravity 1016. Resembles milk. Reduces Nylander's reagent, becoming dark brown at first and later quite black. Fehling's solution gives a red deposit. Urea present, 2 gr. per oz. The fluid contained a very large quantity of albumen, becoming solid on boiling with the addition of acid. Large numbers of granules present in centrifuged deposit which are unaffected by Scharlach."

(2) "*Ascitic fluid.*—Second examination. Specific gravity 1013, alkaline reaction. Fluid shaken up with osmic acid and with Scharlach gave no evidence of fat. Fluid became almost solid on boiling after the addition of acetic acid. Saturation with magnesium sulphate precipitated all the proteids, and fluid was clear after filtration. Albumins and globulins both present in about equal proportions. On digesting the fluid with trypsin at 37° C. albumoses and peptones were both present. The fluid was filtered through a Chamberland porcelain filter, and the filtrate was almost clear. This was boiled with the addition of acetic acid and showed a small trace of albumen. Carbonates and phosphates present in the filtrate. Crystals of phenyl glucosazone obtained. On agitating with ether the turbidity of the fluid was removed, and it gradually became gelatinous. The ethereal extract showed the presence of fat in small quantities. Saponification of the original liquid was obtained. On the addition of xylol and chloroform to the original liquid a dense precipitate was obtained."

(3) "Clear, slightly alkaline. Specific gravity 1016. A faint trace of albumin by the boiling test. A slight flocculent precipitate on saturation with magnesium sulphate. A reducing substance is present. Carbonates, phosphates, and urea found (less than 1 gr. per oz.). On agitation with ether no change was observed. On the addition of xylol and chloroform a dense white precipitate occurs.

(*a*) *Ascitic fluid. Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Endothelial cells | 393 | 78·6 |
| Small lymphocytes | 97 | 19·4 |
| Large hyaline cells | 10 | 2·0 |
| | 500 | 100·0 |

Eighteen c.c. of the above fluid were inoculated intra-peritoneally into a guinea-pig. When the animal was killed six weeks later there was no evidence of peritonitis,[1] and all the organs appeared healthy on macroscopic examination.

*Peritoneal fluid. Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Finely granular polynuclear cells | 230 | 46·0 |
| Small lymphocytes | 132 | 26·4 |
| Large lymphocytes | 10 | 2·0 |
| Endothelial cells | 128 | 25·6 |
| | 500 | 100·0 |

*Post-mortem examination.*—Sections of the liver, spleen, and glands were submitted to microscopical examination and found to be normal.

(*b*) *The pleural effusion.*[2] *Differential count of* 400 *cells:*

| | | Per cent. |
|---|---|---|
| Small lymphocytes | 370 | 92·5 |
| Large lymphocytes | 3 | 0·75 |
| Coarsely granular polynuclear cells | 1 | 0·25 |
| Degenerated cells | 25 | 6·25 |
| Finely granular polynuclear cells | 1 | 0·25 |
| | 400 | 100·00 |

Unfortunately, not sufficient fluid was obtained for inoculation.

Case 42.—H. M—, female, aged 59 years. The patient's father died of phthisis.

*Present history.*—Fifteen months ago she first noticed that the abdomen was increasing in size. A medical man removed "twelve quarts" of fluid, and after paracentesis a large swelling on the right side of the abdomen was found. The fluid quickly reaccumulated and was again removed. One year ago she was operated on, and a multilocular ovarian cyst successfully removed.

*Present illness.*—Two months before admission she found she was getting thinner, and that the abdomen was increasing in size. There was pain in the back associated with some vomiting. On physical examination it was found that the abdominal cavity contained a large quantity of free fluid. On dipping no definite hard structures were to be made out. Paracentesis was per-

[1] There was probably some pathological condition to account for the presence of 46 per cent. of polynuclear cells.

[2] The patient subsequently developed pleurisy.

formed, and 18½ pints of dark fluid were removed. The liver edge was palpable below the costal margin afterwards, but no tumour was detected. The heart and kidneys were normal, and there was an absence of alcoholic taint.

*Progress of case.*—The fluid slowly reaccumulated, and a further quantity of 14½ pints was removed at a second operation. As before, nothing abnormal was found in the abdomen after paracentesis. The fluid is now slowly reaccumulating for the third time.

*Temperature-chart.*—There was a distinct tendency to a subnormal temperature in the morning, and in the evening there was not infrequently a rise to 99° F. The patient has been under observation for nearly eight weeks, and is still in hospital.

*Pathological aspect of the case.*—Eighteen and a half pints of non-viscid, dark fluid were obtained. Microscopically blood-cells and large granular cells were present, and on boiling a large quantity of albumen was found. The specific gravity was 1022. A second examination was made on a further sample with the same result.

*Differential count of* 500 *cells:*

| | | Per cent. |
|---|---|---|
| Endothelial cells | 485 | 97·0 |
| Small lymphocytes | 12 | 2·4 |
| Finely granular polynuclear cells | 3 | 0·6 |
| | 500 | 100·0 |

The endothelial cells in this case were notable for their extraordinary size. Many of them showed two or more nuclei. Thirteen examples presented a typical large hyaline nucleus, but the protoplasm resembled that of the endothelial cells. No mitosis was seen. Cells three or more times the normal size were common, and a few still larger were observed. No evidence of malignancy present.

Case 25.—R. B—, male, aged 37 years. No family history of tuberculosis was obtained.

*Present illness.*—The patient had had rheumatic fever (several attacks) and there was a history of alcohol. Previous to admission he had noted swelling of the abdomen and complained of attacks of colicky pain accompanied by diarrhœa. On examination a large quantity of free fluid was present in the abdominal

cavity; the liver edge could not be felt. Paracentesis was performed and 10½ pints of fluid were obtained.

*Progress of case.*—The liver was not palpable after removal of the fluid. At a second operation 12 pints 13 oz. escaped. After this the abdomen did not again fill up and the patient was discharged in a fair state of health.

*Temperature-chart.*—There was no pyrexia.

*Pathological aspect of the case.*—The fluid removed was darkish brown and quite clear. The specific gravity was 1012 and the reaction alkaline. Albumen was present. At the time of paracentesis the temperature was normal.

*Differential count of* 163 *cells:*

| | | Approx. No. per cent. |
|---|---|---|
| Finely granular polynuclear cells | 40 | 24 |
| Small lymphocytes | 55 | 33 |
| Large lymphocytes | 15 | 9 |
| Coarsely granular polynuclear cells | 11 | 7 |
| Endothelial cells | 42 | 26 |
| | 163 | |

## Summary and Conclusions.

(1) In spite of some anomalies and certain discordant results the cytology of pathological fluids is of considerable value in the diagnosis of disease.

(2) It is absolutely necessary that all films should be prepared from the fresh fluid and that a reliable staining reagent be used. Leishman's stain is by far the most suitable.

(3) A predominance of small lymphocytes in a pleural or peritoneal exudate points to tuberculosis with but few exceptions. The percentage of such cells in the pleural fluid is usually very high.

(4) An excess of small lymphocytes in the cerebro-spinal fluid of a child is characteristic of tuberculous meningitis, provided that syphilitic meningo-encephalitis be excluded.

(5) The comparatively high percentage of polynuclear cells stated by Widal and others to be present in the early stages (?) of tuberculous meningitis is not a constant phenomenon. Many cases show only lymphocytes from the first.

(6) The term "pseudolymphocyte" is highly misleading and should be discontinued.

(7) Cytodiagnosis in disease of the nervous system is chiefly of value in obscure cases and as an aid to the differentiation of organic from functional disease. In most instances a lymphocytosis of the cerebro-spinal fluid points to a syphilitic nervous lesion, but not in all, as it is well known that lymphocytosis occurs in most organic nervous conditions.

(8) Cytodiagnosis is very rarely of value in malignant disease.

(9) In acute infective inflammation of the serous membranes the fluid consists almost entirely of finely granular polymorphonuclear cells.

(10) The endothelial cell is pathognomonic of mechanical effusions into serous cavities, but such effusions may be due to very different causes and the above statement only applies to uncomplicated cases.

(11) An excess of endothelial cells excludes tuberculosis or acute infection with pyogenic micro-organisms.

(12) In the very early stages of peritoneal tuberculosis in animals the peritoneal fluid may appear normal, but if time be given a lymphocytosis will develop. This fact emphasises the necessity for a complete histological examination of all the organs, and the mistake of trusting to macroscopic evidence alone.

(13) It will be unnecessary in future to have recourse to animal experiments to prove the existence of tuberculous pleurisy if a well-marked lymphocytosis has been obtained.

(14) I fully agree with the following remark of Dr. Turton: "I contend that in no case should a diagnosis be based wholly on the result of the cytological examination, but this should form merely a valuable link in the chain of clinical evidence."

Drs. S. J. Sharkey, T. D. Acland, H. P. Hawkins, H. G. Mackenzie, H. G. Turney, and J. J. Perkins have all granted me permission to make free use of the cases under their charge at St. Thomas's Hospital, and to them my best thanks are due.

Had not Mr. L. S. Dudgeon kindly performed all the animal experiments for me, the section on tuberculous pleurisy, the principal subject of my research, would have been incomplete and wholly inadeqate to the importance of this particular lesion.

I have to acknowledge the courtesy of Dr. H. Harwood Yarred, Resident Assistant Physician to St. Thomas's Hospital, and the House Officers of the past year for affording me every facility while collecting material from the wards.

Dr. W. O. Meek has been good enough to furnish me with particulars of two cases which came under his observation while acting as house physician at the Bromptom Hospital, and one of my paintings was made from a preparation in the possession of Dr. Philip Panton. In addition to the four paintings there are three illustrative photomicrographs for which I am indebted to my friend Mr. J. W. Silva.

*May 29th*, 1906.

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## 21. *Acute lymphocythæmia.*

By F. G. Bushnell.

E. H—, aged 43 years, bricklayer, married. Has four children alive and healthy, one died just after birth. Admitted November 22nd, 1905, under the care of Dr. E. Hobhouse. His wife has had one miscarriage.

For twenty years or so he has been liable to pain in abdomen. He thinks the pain at times is caused by food, this coming on about one hour after meals, and sometimes associated with diarrhœa. He has never suffered from vomiting and never from malaria. He drinks about a pint of beer daily, but no spirits as a rule. The bowels are open daily; occasionally he has diarrhœa.

The present illness began in September. It came on suddenly, with pain in upper abdomen after a big meal of potato-pie. The pain lasted for twenty-four hours. He saw a doctor, who gave him medicine, which relieved him. He tried to resume work, but was too weak and short of breath. Since then the attacks of pain have returned about twice a week, and lasted twenty-four hours or so, on ordinary diet. The last attack was on November 19th, and since then the bowels have not been open. Recently the motions were dark-coloured.

On *admission*, pale and waxy appearance, lips pallid and crusted with brown material. Tongue pale, but fairly clean. Teeth and gums covered with brown crusts. *Abdomen*: Not distended, spleen reaches 1½ inches beyond costal margin. There is a resistance in right hypochondrium, but no definite tumour. *Respiratory system*: The entry of air at right base and axilla is poor. *Circulatory system*: H.A.B. in sixth space in ? nipple line.

Systolic murmur loudest in pulmonary area, and ? a valvular. There is a short diastolic murmur, heard best in third left space. *Glandular system*: There are some shotty, small glands in left cervical region. The axillary glands are palpable, but not the iliac or femoral glands.

*Post-mortem examination.*

E. H—, aged 43 years, died November 27th, 1905. Date of admission November 22nd, 1905. *Post mortem* November 28th, 1905, by Dr. Reynolds. There is slight green discoloration on right groin; rigor mortis is marked.

*Clinical summary.*—Eight or nine weeks ago suffered from pain in upper part of abdomen following a meal of potato-pie. Pain recurred in one or two weeks. No melæna, no hæmaturia; wasted considerably lately. Spleen enlarged, double aortic murmur, lumps in both loins ? fæces, marked pulsation in abdominal aorta, with systolic thrill, sudden collapse, ? hæmorrhage.

Development, good; nourishment, poor; complexion, light; no dropsy present.

*Brain and spinal cord.*—No examination made.

No enlargement of cervical glands on right side, very slight on left, none of thyroid, thymus not recognised.

*Pleuræ.*—No adhesions; no fluid in pleural cavities.

*Lungs.*—Slightly œdematous and emphysematous.

*Pericardium.*—Not thickened, contains 38 c.c. clear fluid.

*Heart.*—Weight, 175 grm. about; somewhat large and flabby. Two "milk spots" 1·5 cm. diameter are present on anterior wall, one at base, other near apex. There are several minute extravasations of blood below epicardium.

*Right side.*—R.A. contains a large ante-mortem clot extending for 6 inches into S.V.C., and for 1 inch into I.V.C. R.V. contains a similar clot, passing for 1 inch into pulmonary artery and also some uncoagulated blood. Both the pulmonary and tricuspid valves are healthy; the ventricle is slightly contracted, the left ventricle is empty and contracted. The mitral valve is healthy; the aortic valve presents slight thickening of corpora Arantii, and is slightly incompetent.

The muscle is *pale, friable,* and fatty. The coronary arteries are slightly atheromatous.

*The thoracic aorta* is *atheromatous*, the abdominal healthy.

The *abdominal parietes* are thin; the peritoneal cavity contains no fluid nor blood-clot.

*Stomach.*—Mucosa pale. The transverse and descending *colon* contain scybala.

The *liver* weighs 2 kilos, is somewhat enlarged, and its capsule is not thickened; it is somewhat fatty, and there is slight venous congestion. No white deposits are seen, but there is a reddish-brown area 1 cm. in diameter in the right lobe about 2 cm. from the upper surface. The thoracic, mesenteric, and retro-peritoneal *lymph-glands* are very slightly, if at all, enlarged, are soft, and greyish-red in colour. The prevertebral hæmolymph glands are not enlarged.

*Spleen* measures 16 × 10 cm., weight 450 grm. (about). There is no sign of perisplenitis or infarctions; the tissue is firm, the capsule and trabeculæ are slightly thickened, the Malpighian bodies are invisible, the pulp is slightly marbled, and of deep chocolate colour in the centre; there are no leukæmic deposits. The suprarenal glands are pale.

*Left kidney* weighs about 175 grms., capsule slips off easily, is slightly enlarged and pale, and the stellar veins are prominent. The cortex and medulla are of normal proportions. There are two small cysts; there are no circumscribed deposits.

*Right kidney* weighs about 160 grms. There are no cysts. On the anterior surface is a whitish area 0·3 cm. in diameter, and *another*, 0·5 cm. in diameter, is seen in a medullary ray.

The *marrow* of the femur and sternum is deep red in colour, but not diffluent, and no circumscribed deposits are seen.

*Blood examination on November 25th*, 1905.

Using Thoma-Zeiss hæmocytometer and my blood "commixer" there were found 1,112,000 erythrocytes to the c.mm. and 69,000 leucocytes. By the Haldane-Gowers instrument the hæmoglobin stands at 20 per cent. The colour index is 0·9. Blood-films stained by Scott's modification of Jenner's staining method show a very large increase of lymphocytes, slightly larger in size and less deeply coloured than the ordinary small lymphocyte. I append a blood-count of over 500 cells, and have attempted to subdivide lymphocytes into small, or the ordinary

lymphocytes; large, differing in size and depth of staining; and large hyaline (these having a somewhat granular and, as it were, fissured nucleus, rounded, irregular, or even lobed). These distinctions are arbitrary, and gradations exist between the three types. The nuclei of these cells often present indentations and irregularities in shape.

No erythroblasts were seen and no megalocytes.

| | Per cent. | Per c.mm. |
|---|---|---|
| Polynuclear neutrophils | 1·0 | 690 |
| Small lymphocytes | 78·3 | 54027 |
| Large lymphocytes | 6·0 | 4140 |
| Large hyaline | 14·4 | 9936 |
| Eosinophils | 0·3 | 207 |
| Mast-cells | 0·0 | 0 |
| Total mononuclear cells | 98·7 | 68103 |

*Microscopical examination of tissues.*

*Methods of fixing and staining.*—The specimens are fixed in 10 per cent. formalin, Orth's fluid, and Flemming's solution. The sections are stained with hæmatoxylin and eosin, or van Gieson and Jenner's solution. This last stain, modified in use by Scott, is as invaluable as Leishman's in distinguishing cells according to their chemical tinctorial affinities. Ferrocyanide of potass, glycerinated iodine, pyronin, and methyl green were also used.

*Lymph-glands* (*lumbar*).—The cortex and medulla is stuffed with lymphocytes, approximating in type to those seen in the blood-stream. The germ-centres of the follicles and secondary nodes are obscured by lymphocytes and the capsule and trabeculæ contain them. In addition, there are fairly numerous neutrophil myelocytes and many large basophil lymphocytes and numerous erythrocytes not confined to vascular channels. There are a few polymorphonuclears and finely granular eosinophile cells. There are numerous plasma-cells throughout the gland and a few mast-cells in and near the capsule and trabeculæ. A giant cell with granular irregular nucleus is seen. The blood-vessels within and without the gland contain many lymphocytes, erythrocytes, and some neutrophilic myelocytes and polymorpho-

nuclears. There are no marked fatty changes, but the fat at the hilum contains lymphocytes. There is no iron reaction given; the endothelial cells are somewhat conspicuous.

The *femoral* lymph-gland is characterised by fair numbers of eosinophile cells and some eosinophile myelocytes with moderate amount of erythrocytes. There are lymphocytes as before, and cells like young normoblasts. Many plasma- and some mast-cells.

A prevertebral *hæmolymph* gland was found packed with lymphocytes and erythrocytes; the nuclei in the former are slightly larger and paler than the ordinary lymphocyte and are round or indented, and contain fine granules or points of chromatin, and frequently the rim of cytoplasm is acidophile. Many large mononuclear cells are scattered through the gland and are frequent in the lymph-sinuses. Some have acidophile or faintly basophil cytoplasms, and some have neutrophilic (myelocytes) or eosinophilic granules. Cells with rather small, clear, pale blue nuclei and narrow rim of acidophile cytoplasms are seen, probably normoblasts. Plasma-cells are found to be present. No mast-cells seen.

*Marrow* (*femur*).—The marrow is of the lymphocytic type, with round or indented, rather pale staining nuclei and faintly acidophile cytoplasm. When staining more deeply there is a close resemblance to normoblasts, which are present. Erythrocytes are numerous, and there are some neutrophilic myelocytes and large mononuclear cells. Giant cells are seen, some with much branched darkly-staining nuclei, others with single or double, irregular, paler nuclei, and acidophile cytoplasm. They are often seen to contain eight or nine blue elements (lymphocytic and erythrocytic) which appear to be engulphed. There are some fine eosinophile cells.

Typical mitoses were not observed, but were not specially examined for.

*Sternum.*—Margin consists at one place of firm fibrous tissue enclosing nests of polyhedral cells with large pale or small dark nuclei. In other places the marrow is lymphocytic. The lymphocytes resemble those of lymph-glands, but there are also numerous large mononucleated cells with purplish cytoplasm and vesicular nuclei, especially numerous along bony trabeculæ, and some neutrophilic myelocytes. There are many giant cells with pink vacuolated cytoplasm and vesicular indented or very irre-

gular, deeply staining nuclei. There are a few eosinophile cells. The capillaries are choked with lymphocytes and others contain hyaline material. The lymphocytes are separated by fine fibrillæ. There are many fragmented nuclei.

*Liver.*—The liver-cells are compressed and vacuolated and have lost their outlines. The capillaries are crowded with lymphocytes and small and large erythrocytes, and, as Mr. Shattock has pointed out, the circulation must be impeded here. Yellow pigment is seen in the cells. Lymphocytes especially crowd Glisson's capsule and are here separated into smaller groups by fine fibrillæ apparently derived from pre-existing connective tissue; foci of lymphocytes and erythrocytes are seen and they are present beneath the capsule. An area 0·6 cm. in diameter is of a cavernous angiomatous nature, divided up into compartments by trabeculæ containing fibroblasts. It contains masses of erythrocytes and normoblasts and lymphocytes in varying proportions. Free around this area are many lymphocytes. Within these spaces are capillaries stuffed with lymphocytes. The lymphocytes resemble those in the lymph-glands. No fat, iron, or glycogen reaction is obtained.

*Kidneys.*—The kidneys contain collections of lymphocytes of 2 mm. downwards. They resemble those in the lymph-glands. *Many* show mitotic and others suggest amitotic activity. The capillaries are crowded with lymphocytes, erythrocytes, and polynuclears, and some doubtful normoblasts. In the collections of lymphocytes fibrillæ appear between the cells. There are a few plasma-cells in the foci of cells. The capsule and vessels are not thickened, and there is no evidence of interstitial nephritis. Some of the urinary tubules imbedded in cells are degenerated, some appear to contain lymphocytes within the epithelial cells. A giant cell with several oval nuclei and granular cytoplasm is seen. The Malpighian bodies contain numerous lymphocytes and erythrocytes within the tuft. Some are shrivelled or concentrically thickened, and the tuft contains large ovoid nuclei. The parenchyma is cloudy. No iron reaction obtains.

*Spleen.*—There is very slight thickening of capsule and reticulum. The Malpighian bodies can hardly be recognised, the pulp being uniformly packed with cells. These are small and large lymphocytes, with round or indented, solid or vesicular nuclei. The large mononuclears have cytoplasm of varying

affinities, neutrophilic or basophilic, and with faint granulations resembling myelocytes. There are a moderate number of finely granular eosinophile and polymorphonuclear neutrophile cells, and some erythrocytes in small numbers. There are numerous plasma-cells about the capsule and trabeculæ. Some large cells contain numerous erythrocytes. Brown pigment is seen, no multinucleated cells and no parasites. The blood-vessels contain lymphocytes.

*Heart.*—The vessels are packed with lympho- and erythrocytes, and lymphocytes crowd the intermuscular septa.

*Pancreas.*—There are intra-acinous and intra-vascular collections of lymphocytes. There is no fibrosis degeneration or

| Pernicious anæmia. | Leukanæmia. | Acute lymphæmia. | Acute myelæmia. |
|---|---|---|---|
| *Blood.*<br>Red cells diminished.<br>Megaloblasts frequent.<br>Poikilocytes, megalocytes, macrocytes present.<br>Hæmoglobin diminished.<br>Colour index high.<br>Slight relative increase of myelocytes.<br>Relative lymphocytosis.<br>Polychromatophilic granular degeneration.<br>Leucopenia.<br><br>Da Costa gives average of myelocytes as 1·8 per cent. in 31 cases; in one case 10 per cent. myelocytes.<br><br>*Marrow.*<br>Markedly megaloblastic in structure. | *Blood.*<br>Red cells as in pernicious anæmia.<br>Lympho or myelocytic leucocytosis.<br><br>*Marrow.*<br>Bushnell and Hall: Very cellular neutrophilic myelocytes, and large and small mononuclear cells, giant cells with rather pale staining neuclei of medium size, and containing vacuoles and round cells. Giant cells with granular cytoplasm and twisted even-staining nuclei. Eosinophile cells few. No fat vesicles, no increase of stroma, normoblasts, erythrocytes, and polymorphonuclears.<br>F. Farkes Weber: No fat vesicles, stroma loose, connective tissue containing blood myelocytes, large and small mononuclears and erythroblasts, the latter in "clusters." Many giant cells. Few coarse eosinophiles. | *Blood.*<br>Erythroblasts uncommon.<br><br>Degeneration, slight or absent.<br><br>Polynuclears, eosinophiles, and mast-cells reduced, often below normal.<br><br>Neutrophilic myelocytes in small numbers.<br><br>Lymphocytes resembling those of normal blood.<br><br>*Marrow.*<br>Neutrophilic myelocytes and less nucleated reds, eosinophiles, and large mononuclears. | *Blood.*<br>Erythroblasts numerous.<br>Polychromatophilic degeneration well marked.<br>Granular degeneration not well marked.<br>Macro-, micro-, and poikilocytes numerous.<br>Leucocytes, polymorphous myelocytes with granules of different affinities present in great numbers.<br>Mast-cells in numbers.<br>Large mononucleated cells present.<br>Polynuclears and eosinophiles relative decreased, but absolutely increased.<br><br>*Marrow.*<br>Few normoblasts, many large and small mononuclears. |

necrosis of pancreas, the isles of Langherhans of which are very distinct.

*The supra-renal capsules.*—The cortical and medullary substances contain collections of lymphocytes within the capillaries. No ganglion-cells were seen.

*The lungs*, unfortunately, were not examined.

I append a comparative table of the conditions of the blood and marrow in pernicious anæmia, leukanæmia, acute myelæmia, and acute lymphæmia.

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22. *Leukanæmia (myeloid splenic anæmia).*

By F. G. Bushnell.

F. H—, aged 25 years, admitted April 28th, 1905, under care of Mr. D. Hall. Father died of phthisis. He has been of yellow colour since three days old. He has often had attacks of pain in upper abdomen, and his motions were grey. The patient gets "rheumatism." He suffers from frequent attacks of epistaxis but not other hæmorrhages. He noticed a lump in abdomen ten years ago, which got bigger. No ascites is present; the spleen fills up the left side of abdomen; the liver is enlarged; the heart is enlarged; the urine has specific gravity of 1015, is acid, has no bile, no albumen; the inguinal glands are slightly enlarged; there is no hair on pubes nor face; the testes are small.

*Post-mortem examination (by F. G. Bushnell), made on August 8th, 1905.*

The weather was hot, the body was examined in the country forty-eight hours after death. *Rigor mortis* was present and signs of decomposition were marked.

The body was thin and ill-developed, the testes the size of common playing marbles, pubic eminence hairless; skin and conjunctivæ were of a yellow colour; the subcutaneous fat was small in amount and yellow; no fluid was found in abdominal cavity.

Thymus gland, relic not seen.

Thyroid gland, not enlarged.

*Lungs.*—No recent tubercle found, but a small calcareous

nodule present in substance of lung; weight of left lung 2 lb. ¾ oz.

*Heart.*—Muscle, pale brown colour, no clots in cavities; mitral valve admits three fingers.

*Pericardium.*—Excess of fluid of brownish colour is present, with reddish sediment.

The *pulmonary artery* contains reddish gelatinous clot; the aorta contains a red and white gelatinous clot.

The *stomach* contains large amount of undigested vegetable matter, skins of beans, etc, but there is no ulceration, etc.

The *liver*, uniformly enlarged, weighs 3 lb. 11 oz., or 59 oz. (Weber's case, 88 oz.), and shows *p.m.* staining. The ducts are dilated and bile-stained; no gross changes are present in parenchyma.

The *gall-bladder* is shrunken, its walls thickened; it contains branching white gall-stones; a probe passes easily from it into the common bile-duct; about 1 drachm of creamy pus has formed in its neighbourhood.

The *pancreas* weighs 8 oz.; nothing noted.

The *spleen* is uniformly enlarged, weighs 2 lb. 10 oz. (42 oz.); on section is red and rather firm; no infarcts present. (In Weber's case weight of spleen was 60 oz.)

The *kidneys* show *p.m.* green colour, left weighs 5½ oz.

The *suprarenal capsules* show nothing noteworthy.

The *testes and prostate* are small.

The *lymph-glands and hæmolymph-glands* are not enlarged, but the former were of reddish colour.

The *marrow* of ribs, sternum, humerus, radius, and ulna was of red colour, increased in amount, but not very firm.

No hæmorrhages present. No evidence of syphilis seen.

*Brain and cord.*—No examination made.

### *Microscopical examination.*

About 150 sections examined.

Tissues were fixed in Orth's solution, Müller's fluid, and Flemming. They were stained with hæmatoxylin and eosin, and by Mann's "long" eosin and methyl blue method. Jenner's stain, as modified by Scott, gave by far the best results for distinguishing blood elements in various tissues. Owing to the

unavoidable delay in obtaining the tissues after death fixation was, unfortunately, imperfect.

The *marrow* showed in all bones a very cellular character and many capillaries, with absence of fat vesicles. Neutrophilic myelocytes (many of small type) and mononuclear cells, most numerous. The former contain nuclei with pale staining nucleoplasm and fine chromatic network. There are numerous giant cells with round, pale staining nuclei of medium size, containg vacuolated areas or remains of cells from two or three to eighteen or twenty, also giant cells with uniformly granular cytoplasm, and twisted, evenly staining nuclei. Few eosinophiles but many polynuclears, lymphocytes, and erythrocytes. There is an excess of normoblasts, but there is no sharp distinction between these cells and lymphocytes. Mitoses are not frequent.

*B. coli communis* was obtained from marrow after death.

The microscopical features of the case are as follows, and a comparative Table is appended with Parkes Weber's case, and Scott's and Telling's case of splenic anæmia in an infant.

F. Parkes Weber.

Male, aged 58 years.

Marrow destitute of fat vesicles, with loose connective tissue containing blood, myelocytes, and large and small mononuclear cells, numerous normoerythroblasts, many with nucleus split up into fragments or droplets. Many giant cells and a few coarse eosinophiles. The fibrous stroma is converted into loose tissue with erythroblasts in clumps.

S. G. Scott and W. H. M. Telling.

Infant, aged 8 months.

*Marrow.*—Blood-cell formation is active and frequent; mitoses, megalo- and normoblasts, myelocytes, "indifferent" lymphoid cells (Wolff,—the basophilic myelocyte of Dominici), small lymphocytes, and polymorphonuclears are present. Mast-cells almost absent.

[Scott considers that transitions were present from large lymphoid cell to neutrophile and eosinophile myelocyte to small lymphocyte and polychromatophilic normoblast.]

*Liver.*—The liver shows a very peculiar condition. The spaces between the hepatic cell columns are choked with cells which, although these are within the intracinous hepatic capillaries,

were not present to such numbers in the blood-stream during life as seen at frequent examinations. As Mr. S. G. Shattock points out, where so existing an impediment to the circulation must exist. The cells consist of normoblasts, with fragmented, bunched, or ovoid nuclei, lymphocytes and granular leucocytes, with twisted fragmented or indented nuclei. Numerous small myelocytes are present and mononuclear cells. The capsule of Glisson shows slight fibrosis, but the duct epithelium is not abnormal.

Such a storage of cells suggests in function either normal marrow or lymph-glands, or the fœtal marrow, liver, or thymus. Somewhat similar, moreover, are the conditions of the spleen and liver in myelo- and lymphocythæmia, in splenic anæmia of infants, and in chronic lead-poisoning, etc.

F. Parkes Weber.

Male, aged 58 years.

The columns of the hepatic cells are separated by cells, myelocytes, large non-granular mononuclears, erythroblasts or their nuclei, eosinophiles and giant cells. The cells were "growth-like."

S. G. Scott and W. H. M. Telling.

Infant, aged 8 months.

Lobular arrangement not clear. No fibrosis, no inflammation. Some of the cells degenerate. In connective-tissue spaces of portal tract and in capillaries throughout the liver are indifferent lymphoid cells with erythrocytes and myelocytes. Mast-cells scanty. A megakaryocyte. [It is a fœtal, hæmopoietic liver with parenchymatous degeneration and injection of bile-capillaries.]

There is golden-brown pigment in the liver-cells which stain poorly and are vacuolated. (There is a "mycelial-like" structure, ? *p.m.* in origin, in the small vessels.)

*Spleen.*—There is a moderate fibrosis of reticulum and trabeculæ and the pulp is stuffed with cells, especially erythrocytes, separating Malpighian bodies, which contain lymphocytes, erythrocytes, and cells resembling normoblasts. The nuclei of the latter are "budding" lymphocytes; cells resembling normoblasts, mononuclear basophile cells and cells with fragmented nuclei are

present in the pulp. Some myelocytes and polynuclears are seen in pulp and Malpighian bodies; the nuclei of the latter are very irregular.

The blood-vessels contain many multi- and mononuclear cells, long, straight bacilli, and a "mycelial-like" structure, ? *p.m.* in origin. Endothelial cells somewhat prominent.

F. PARKES WEBER.

Male, aged 58 years.

Malpighian bodies normal. Pulp permeated by erythroblasts, mononuclears, and coarse eosinophiles. These and erythrocytes are equally distributed throughout pulp, except where they occur without erythrocytes in "clumps."

S. G. SCOTT AND W. H. M. TELLING.

Infant, aged 8 months.

No fibrosis, no degenerative change. The organ is packed with erythrocytes and various kinds of leucocytes. The Malpighian bodies appear to be normal at their centre, but at periphery there are "indifferent" lymphoid cells, neutrophile and eosinophile myelocytes. These cells and many red cells and normoblasts are a striking feature. The endothelial cells are not prominent, nor is there evidence of blood-destruction.

*Lymph-gland.*—A gland from gastro-hepatic omentum shows fibrosis and fibroblasts, degenerative changes, necrotic areas, and giant cells with peripheral nuclei. The germ-centres contain lymphocytes and numerous erythrocytes. Much pigment present. Bacilli present. A bronchial lymph-gland shows fibrosis and pigmentation.

*Pancreas.*—Degenerative changes, but no cells similar to those in liver. Bacilli present.

*Kidneys.*—Parenchymatous degeneration, no cell collections.

*Thymus, thyroid, supra-renal capsules, stomach, intestines.*—Not examined.

*Gall-bladder* shows destruction of mucosa and infiltration of wall with round cells.

No iron or amyloid reaction was obtained in any viscus.

F. Parkes Weber.

Male, aged 58 years.

Hæmolymph-glands contain cells similar to those in splenic pulp.

Pancreas, not diseased.

Kidneys, nothing noteworthy.

S. G. Scott and W. H. M. Telling.

Infant, aged 8 months.

Lymph-glands have undergone complete transformation into red bone-marrow, showing all stages of blood-cell formation. Giant-cells are present (megakaryocytes of Dominici). There is phagocytosis by the latter and by the endothelium of sinuses. Pigment.

Thymus does not show myeloid transformation.

| | White. | Red. | Hæmoglobin. | Index colour. | Polymorphonuclears. | Eosinophile polymorphonuclears. | Myelocytes. | Intermediate. | Small lymphocytes | Large lymphocytes | Mast-cells. | Normoblasts. | Megalo-blasts. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Per c.mm. | Per c.mm. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. |
| May 3 | 9300 | — | — | — | — | — | — | — | — | — | — | — | — |
| „ 6 | 11000 | 1,120,000 | 15 | 0·7 | 60·8 | 1·2 | 1·6 | 4·6 | 23·1 | 6·5 | 0·6 | 7 | 1 |
| „ 13 | 6400 | — | — | — | — | — | — | — | — | — | — | — | — |
| June 3 | 2400 | 1,280,000 | 25 | — | 64·8 | 3·1 | 6·8 | 1·8 | 28·3 | — | 0·6 | Present | |
| „ 10 | 3800 | 1,736,000 | 20 | 0·58 | — | — | — | — | — | — | — | — | — |
| „ 16 | 5750 | 1,280,000 | 25 | 1·0 | — | Same characters as before present. | | | | | | | |
| „ 23 | 2200 | 1,840,000 | 22 | 0·6 | — | „ | | „ | | „ | | „ | |

## Remarks on the Cases of Acute Leucocythæmia and Leukanæmia.

These cases well exemplify uncommon types of diseases of the blood-forming tissues, and illustrate the extent and interdependence of the latter. Our cases show well that acute lymphocythæmia is characterised by an enormous relative and absolute increase of small and large lymphocytes in the blood, and by lymphocytic lesions in the bone-marrow, in the spleen, and to a less extent in the lymph-glands, liver, and other organs. One sees also that leukanæmia (splenic myeloid anæmia) presents as features an anæmia in the red cells resembling that of pernicious anæmia and changes in the colourless cells allied to myelæmia,

but distinct (in pernicious anæmia slight myelocythæmia is described). The marrow, spleen, and liver are affected by myeloid changes. A word on the hæmopoietic system may be opportune. As to its component parts, certain observers hold that there is no good evidence of the formation of red cells in the spleen or hæmolymph-glands in adults either in health or in disease (1). Yet Aubertin views the system as formed of three unequally differentiated tissues, and he believes that alterations arising in one tissue generalise to the two others. Thus in myeloid leukæmia the spleen, bone-marrow, and lymph-glands are equally myeloid, in chronic lymphatic leukæmia there is lymphoid hyperplasia of all three tissues, and in acute lymphocythæmia the lesions are most marked in the bone-marrow, less so in the spleen, and little in the lymph-glands (2). This is seen in these cases. In the fœtus it is well known that nucleated red cells are found in the liver, spleen, and elsewhere, as in the adult they occur in the bone-marrow. Other observers, again, record instances of the spleen, or liver, or lymph-glands participating in blood-cell formation (6). There is evidence too in these diseases of the common origin of blood elements. It is believed by some that leucocytes and erythrocytes have one ancestor, a lymphoid cell, from which it is certain that granular and non-granular leucocytes are derived in the fœtus (Pappenheim).

Especially in chronic myelocythæmia is the familiar polymorphism of the leucocytes a confirmation of the common origin of lymphocytes, for all forms are seen, transitional between large lymphocytes, myelocytes, and polymorphonuclears. I have seen in a case of this disease, under the care of Dr. W. H. Broadbent, cells of the type of large lymphocytes to be replaced by myelocytes, judging from the appearance of neutrophilic granulations on different occasions appearing in the vast proportion of cells present (3). Dr. Browning (4) and Dr. Williamson have also recorded cases in which enormous numbers of large lymphocytes may be present in the blood; at other times these cells are seen, but with the faintest granulations visible, and on another occasion myelocytes in similar profusion. If this is so, acute myelæmia and acute lymphocythæmia, though dissimilar in type, are in origin related to one another. In this respect it is of interest to note that in one case of acute lymphocythæmia there were

eosinophile cells and eosinophile myelocytes in the marrow, in the lymph-glands, and even in the spleen—evidence perhaps of a common marrow origin of these elements. In another case of acute lymphocythæmia examined by Professor Muir, under the care of Parkes Weber, Eastes found 3·6 per cent. of eosinophilic myelocytes in the blood (Dudgeon).

It seems, then, as if the markedly lymphocytic marrow of acute lymphocythæmia is largely the origin of the lymphocytes in that tissue, but it is clear that it may be supplemented by the spleen and lymph-glands, possibly even by the liver and by other viscera.

In leukanæmia (as also in myelocythæmia) similarly the manufactory of the myelocytes is the marrow, supplemented by the spleen and liver and perhaps the lymph-glands. Vaquez and Auberton say of this disease: "Dans la première affection il y a une suractivité myéloide de la rate specialisée vers la serie blanche, tandis qu'elle est spécialisée vers la serie rouge dans la seconde" (5).

The phagocytic action of the giant cells in the case of leukanæmia suggests that the elements ingested had either been sensitised by some "opsonin" or the cells stimulated by a "stimulin." In the absence of evidence of hæmolysis in the tissues the disease, it is fair to conclude, is primary in the marrow; but experimental proof is needed. In our case of acute lymphocythæmia and in those of Bradford and Batty Shaw (7) there was a bacterial infection of long duration, and their products in the blood-streams may have had a selective action on certain elements of the marrow and blood-forming tissues. Proliferation of cell elements in marrow occurs in infections, as in smallpox (myelocytic), as in polynuclear reactions, or as in eosinophilic reactions (8), and Jousset claims that myeloid leukæmia is parasitic in origin (9). Banti would explain the leukæmic condition as one of tumour-formation, with or without erosion of small vessels of marrow (10). On the one side it is a problem of blood-cell physiology and pathology and of the life-history of the blood-forming organs, and on the other of a factor, possibly of the nature of a biochemical product, acting in small doses over a long period, which affects the reproductive activity of the cells in question.

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*February 20th,* 1906.

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## 23. *Therapeutic inoculations in Mediterranean fever.*

By Staff-Surgeon S. T. REID.

ONE has only to glance at the literature of the therapeutics of Mediterranean fever to see that drug treatment has failed completely, and however effective antiseptics may be in killing the *Micrococcus meletensis* in the test-tube, when introduced into the system their benefit is *nil.*

Wright's name will always be associated with the adaptation to clinical methods of the principle that the dead organism introduced into the body in suitable doses stimulates a responsive production of protective substance. The discovery of the opsonic power of the blood has given a means of accurately regulating the dose of the vaccine to be inoculated, and also the amount of good resulting therefrom.

*Technique.*—The method used is that described by Wright and Douglas ('Proc. Royal Society,' vol. lxxiii, No. 490), and modified by them into using equal volumes of: (1) patients' serum; (2) washed corpuscles; (3) emulsion of *M. meletensis.*

The experience gained in doing many hundreds of opsonic measurements of Malta fever serum may be useful in pointing out some of the pit-falls the novice is likely to fall into.

(1) *Salt content.*—It is very necessary to be careful of the salt content of the opsonic mixture when comparisons are made between normal and immune sera. If an emulsion of the *M. meletensis* is made in a 1·5 per cent. of sodium chloride the following results: (1) An immune serum will register a much higher opsonic count previous to inoculation; (2) subsequent to inoculation the opsonic measurement will remain the same for three or four days, then suddenly shoot up to two or three times the normal, then rapidly fall within forty-eight hours. This is very different from the classical curves in which, after a preliminary fall (negative phase), the opsonic measurement rises to 1·6, and remains at that for four or five days.

(2) *Culture.*—Muir and Ritchie point out that the bacillary forms of the *M. meletensis* may be obtained in young cultures. Another important fact is that the younger the culture the better it stains.

In order to benefit from these facts the following routine is practised: (1) Spread a very small amount of the culture over the whole surface of an agar tube as evenly distributed as possible; (2) grow for twelve hours in a warm incubator and leave on bench for another twelve hours (the length of time left in the incubator must be regulated by the growing power of the particular strain of *M. meletensis*); (3) scrape off by means of a small glass pipette the resulting growth, and emulsify.

*Stain.*—Any stain will do that will colour the coccus dark and leave the granules of the leucocyte unstained, at the same time giving the outline of the latter. Carbo-thionine has proved much the most successful in my hands, the only difficulties are that it is erratic, deteriorates, and has to be prepared carefully.

*Process.*—(1) Do not fix; (2) pour the stain on the slide and leave for ten seconds; (3) wash off with tap-water till the film has a reddish tinge.

*Preparation and dose of vaccine.*—Ordinary agar tubes are planted with the *M. meletensis* and grown for three days. The area of superficial growth is taken in square centimetres. The whole growth is emulsified in broth or salt solution in such proportion that 1 c.c. = one third square cm. of growth. It is possible

to enumerate the number of cocci per c.cm. according to the method of Wright; this, however, is very tedious work, and there is no necessity for its adoption. This emulsion is heated in a bath at 65° C. for half an hour, left in the incubator, and finally tested to see whether it is sterile or not.

*Dose.*—One sixth to one third of a square centimetre's growth is a very workable guide.

Thirty-six inoculations are recorded below, with the beneficial results following each, under the respective headings.

*Temperature.*—In most cases the first effect of inoculation is to raise the temperature; this corresponds to the negative phase, and never lasts more than forty-eight hours. Chart III, G. M—, illustrates this point. The result of inoculating about 600,000,000 *M. melentensis* is that the temperature rises from 102°, and becomes 104° for two evenings. Chart II, G. L—, also illustrates this point in a slighter degree.

As soon as the system responds and produces protective substances the temperature drops, and in most cases becomes normal. The effect on the temperature is well illustrated by Chart I, J. G—.

INOCULATIONS (36).

| | Decrease of temperature. | Decrease of temperature. Relief of pain. | Decrease of temperature. Increase of weight | Increase of weight. | Relief of pain. | Relief of orchitis. | No Result. |
|---|---|---|---|---|---|---|---|
| G. A— | — | 1 | — | 1 | — | — | — |
| W. A— | — | — | — | 1 | 2 | — | — |
| W. C— | 1 | — | 1 | — | 1 | — | — |
| W. D— | — | — | — | 1 | 1 | — | — |
| M. E— | 3 | — | — | 1 | — | — | 2 (acute stage) |
| J. G— | 1 | — | — | — | — | — | — |
| N. H— | — | 1 | 1 | 2 | — | — | — |
| W. J— | — | 1 | — | 1 | — | — | — |
| G. L— | — | — | 1 | — | — | — | — |
| J. L— | — | 1 | — | — | — | — | — |
| E. M— | 1 | — | — | — | — | 3 | 1 (small dose) |
| G. M— | 1 | — | — | — | — | — | — |
| G. R— | — | — | — | 1 | — | — | — |
| W. S— | 2 | — | — | — | 2 | — | — |
| Total | 9 | 4 | 3 | 8 | 6 | 3 | 3 |

Two undulations of pyrexia are shown occurring in August—a third commencing on October 1st is cut short by inoculation.

Charts II and III, G. L— and G. M—, show the beneficial effect of inoculation.

Altogether in nine cases out of the fourteen recorded, a fall of temperature was noted.

It is easy to understand the effect of inoculation on a strictly localised condition such as acne or lupus by the introduction into the system of the causa-causans of these lesions, and so producing a constitutional reaction.

In the above cases we have a very different state of affairs, the patients being in a septicæmic condition, suffering from pyrexia produced by the poison of the organism. Yet such is the complicated mechanism of immunisation that a further introduction of the same poison into another part of the body rapidly cuts short the fever. This fact, in combination with work done by Wright and Douglas, opens up the whole field of therapeutics by inoculation, and demonstrates that in all cases of bacterial invasion, be they acute or chronic, this method of treatment is beneficial.

*Pain.*—Under this head are recorded cases in which pain is the chief symptom. They are nearly all cases of the so-called "neuritis." Four cases are recorded in the "table of inoculations" (col. 2) in which decrease of temperature accompanied the relief of pain. Six cases (col. 5) relief of pain only.

*Nutrition.*—To those who know anything of Malta fever little need be said of the condition of the majority of the patients subsequent to an attack of "fever." Anæmia, debility, and repeated attacks of the condition misnamed "neuritis" make life a misery. The duration of temperature may be measured by months, while these symptoms remain for years and are generally considered as sequelæ of Malta fever. Sir A. E. Wright has demonstrated the *M. meletensis* in the spleen and muscular sheaths years after the so-called attack of "Fever."

A new term is wanted to describe the debilitated condition in which the patient is obviously suffering from the presence of the *M. meletensis* in the system. "Meleteria" or "meleteriosis" are hardly coinable words, and perhaps it does not matter what term is used so long as it is recognised that patients in this con-

dition are the subjects of a particular bacterial invasion, and that the proper vaccine is used for their treatment.

Chart IV, W. D—, shows a case admitted to Royal Naval Hospital, Chatham, on January 18th, 1906, in this "meleteric" condition with practically no pyrexia. Inoculated on January 19th his weight increased from 121 lbs. to 126½ lbs. on February 1st, and finally became 129 lb. on March 3rd. The relationship between the weight and opsonic curves is very interesting. Chart II, G. L—, gives an illustration of this.

N. H— is another case in which the improvement in nutrition was very marked subsequently to inoculation.

The "table of weights" gives the gain of weight per day of seven cases out of the fourteen that had been inoculated.

TABLE OF WEIGHTS.

| Initials. | 1st weighing. | | 2nd weighing. | | Gain, lbs. | Days. | Gain per day, lbs. | Remarks. |
|---|---|---|---|---|---|---|---|---|
| | Date. | lbs. | Date. | lbs. | | | | |
| W. A— | 15/8/05 | 138 | 31/8/05 | 148 | 10 | 16 | 0·6 | — |
| G. A— | 19/1/06 | 139 | 1/2/06 | 147 | 8 | 13 | 0·6 | — |
| W. C— | 12/9/05 | 131 | 20/9/05 | 137 | 6 | 8 | 0·7 | — |
| W. D— | 22/1/06 | 121 | 1/2/06 | 126½ | 5½ | 9 | 0·6 | — |
| M. E— | 16 11/05 | 156 | 1/12/05 | 165 | 9 | 15 | 0 6 | — |
| N. H— | 15/8/05 | 136 | 7/9/05 | 152 | 16 | 23 | 0·7 | — |
| G. R— | 15/3/06 | 154 | 26/3/06 | 160 | 6 | 11 | 0·5 | — |

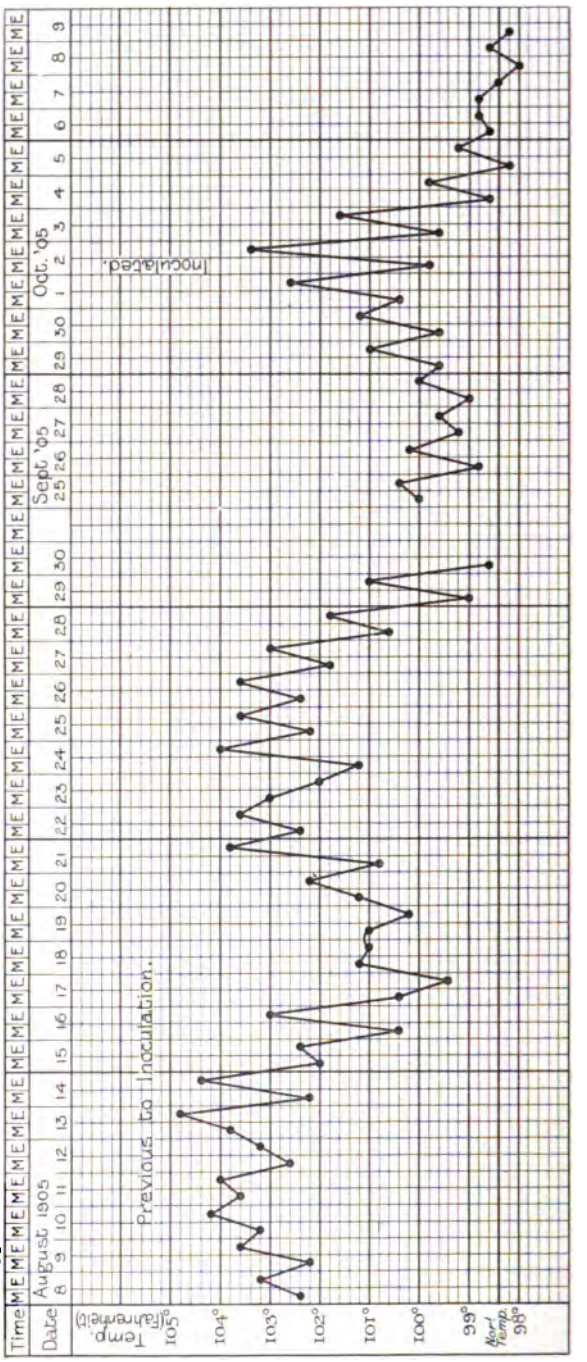
A study of this table shows that the following conclusion is justified: That giving a subject debilitated from meleteric infection, inoculation, in proper dosage, will produce such an improvement in the nutrition of the patient that his weight will record a gain of at least half a pound a day.

Since such marked benefit results from therapeutic inoculation of Malta fever, we may, with advantage, turn our attention to the much larger question of preventive inoculation.

The last results of anti-typhoid inoculations are so very conclusive that the method is now established as a means of the prevention of typhoid.

The adoption of this method of prevention of Malta fever would lead, I feel sure, to a saving of many thousands of pounds yearly to the nation, to say nothing of the comfort and health of the troops in that Mediterranean island. *April 3rd*, 1906.

CHART 1.




The chart shows two undulations of pyrexia untreated (August), and a third one (October) cut short by inoculation.

CHART 2.

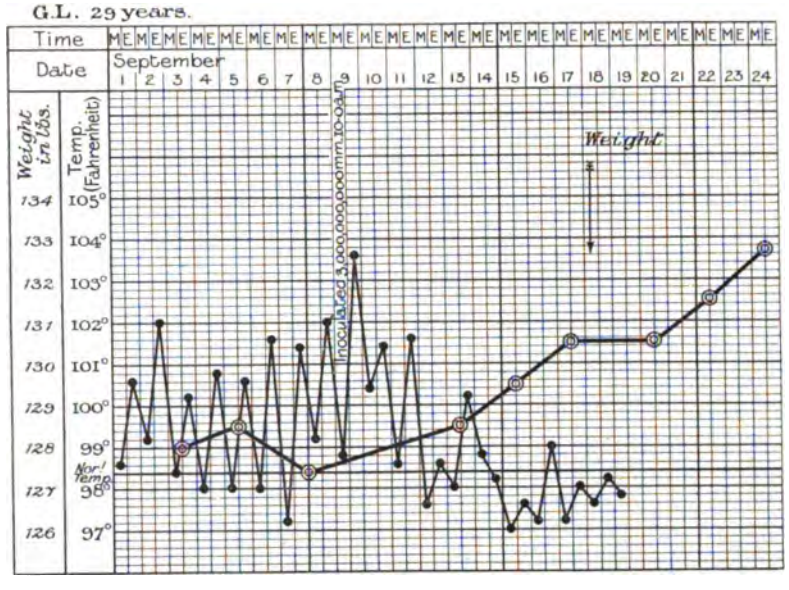
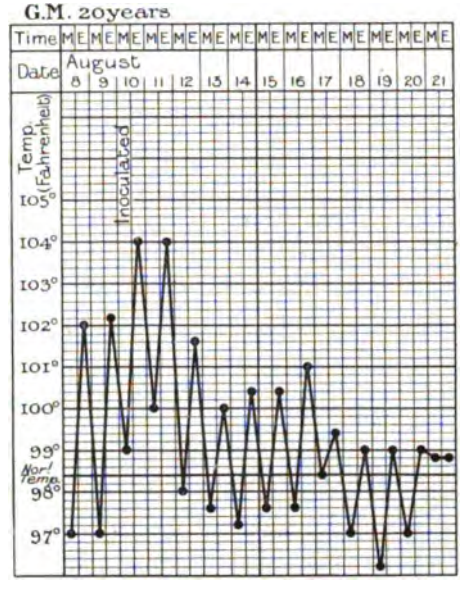
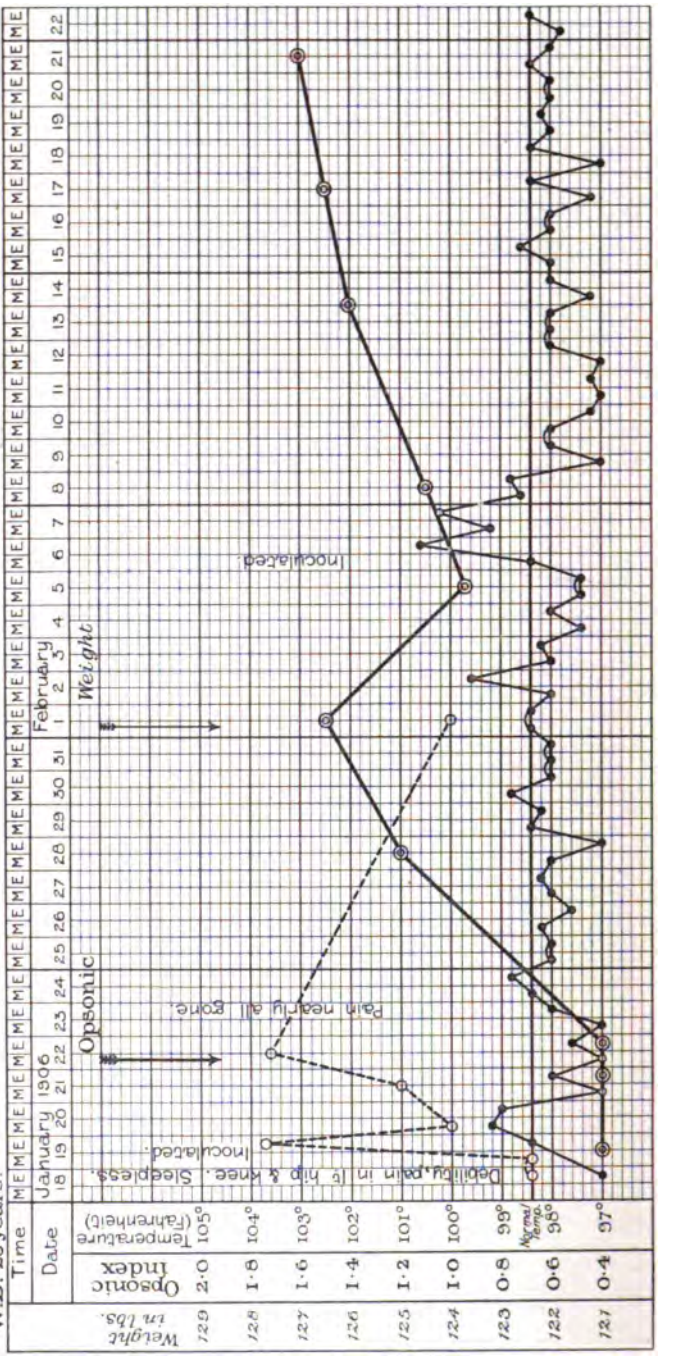



CHART 3.




The charts show the effect of inoculation on the pyrexia. As a direct result, the temperature is raised (negative phase); subsequently it falls and becomes normal.

CHART 4.




The chart shows the effect of inoculation on a subject debilitated from Mediterranean fever. The manner in which the weight curve (continuous line) follows that of the opsonic curve (dotted line) is noteworthy.

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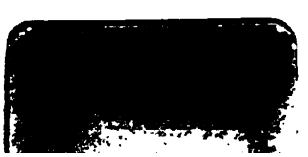
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